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Target long-term responders in indolent non-Hodgkin's lymphoma: ^{90}Y-ibritumomabtiuxetan

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A B S T R A C T

Yttrium 90 (^{90}Y) ibritumomab tiuxetan (Zevalin), a radiolabeled monoclonal antibody against the CD20 antigen, is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma (NHL) in the USA, including patients with rituximab-refractory follicular NHL. Data on 211 patients treated in 4 registrational USA clinical trials were analyzed to determining the number and characteristics of patients achieving long term durable responses and compare the efficacy and safety of ^{90}Y ibritumomab tiuxetan when it was used after the first relapse of NHL and when it was used after 2 or more prior therapies. Sixty-three of the patients (30%) were treated with ^{90}Y ibritumomab tiuxetan upon their first relapse and 148 (70%) after 2 or more prior therapies. TTP of ≥12 months was noted in 78 patients (37%) who were termed long term responders and were further characterized. Median age of the long term responders was 58 years (range 24-80) with 44% over 60 years. Notably, 59% Of patients had received ≥2 prior treatments and 37% had failed to respond to immediate prior therapy. Median response duratin was 28.1 months (10-5-80.3 months). Median TTP was 53.9 months. If analyzed by number of prior treatments in the overall population, the complete response rate (confirmed [CR] and unconfirmed [CRu]) was higher in first-relapse patients (49% vs. 28%; p<0.01), and the median time to progression (TTP) was longer (12.6 vs. 7.9 months; p< 0.05). In patients with follicular NHL the differences were even more pronounced (CR/CRu: 51% vs. 28%; p<0.01; TTP: 15.4 vs. 9.2 months; p <0.05). Yttrium 90 ibritumomab tiuxetan has substantial clinical benefits and can induce durable long term responses in patients with relapsed/refractory B–cell NHL. Failure to respond to prior therapy does not preclude achieving a long-term remission, although the likelihood for such an occurrence is higher for patients treated in first relapse.

Radioimmunotherapy (RIT) has emerged as an important treatment option for patients with B-cell non-Hodgkin's lymphoma (NHL). The first commercially available RIT agent for cancer, yttrium 90 (^{90}Y) ibritumomab tiuxetan (Zevalin), was approved in the United States in February 2002 and is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL, including patients with rituximab-refractory NHL.[1]

Yttrium 90 ibritumomab tiuxetan consists of ibritumomab, a murine monoclonal immunoglobulin G1 kappa antibody to CD20, a surface antigen that is expressed on 90% of B-cell lymphomas,[2] conjugated to the metal chelator tiuxetan for retention of the beta emitter ^{90}Y for therapy or indium 111 (^{111}In) for imaging (Figure 1). Thus, treatment with ^{90}Y ibritumomab tiuxetan targets radiation to B-cell lymphomas, which are inherently sensitive to radiation.[3]

The pharmacokinetics of ^{90}Y ibritumomab tiuxetan show minimal interpatient variability; dosing is based on patient weight and platelet count rather than dosimetric or pharmacokinetic measures.[4,5] The dose-limiting toxicity of ^{90}Y ibritumomab tiuxetan is transient myelosuppression, which is usually most pronounced at 7 to 9 weeks after the therapy and resolves within 1 to 4 weeks.[6] Yttrium 90 ibritumomab tiuxetan is not associated with the degree of nausea, vomiting, alopecia, and mucositis that is seen with conventional chemotherapy for NHL.[6,7]

The overall response rates (ORRs) in 4 registrational trials of ^{90}Y ibritumomab tiuxetan were high (73%–83%), with the ORR in patients with follicular NHL being as high as 85%.[8] There were long-term durable remissions (time to progression [TTP] ≥12 months) in 37% of patients,[8-13] some of them longer than 75 months.[8] In a long-term follow-up of the phase 1-2 dose-finding trial patients with responses according to the International Workshop Response criteria (IWRC) had a median TTP and duration of response (DR) of 12.6 months and 11.7

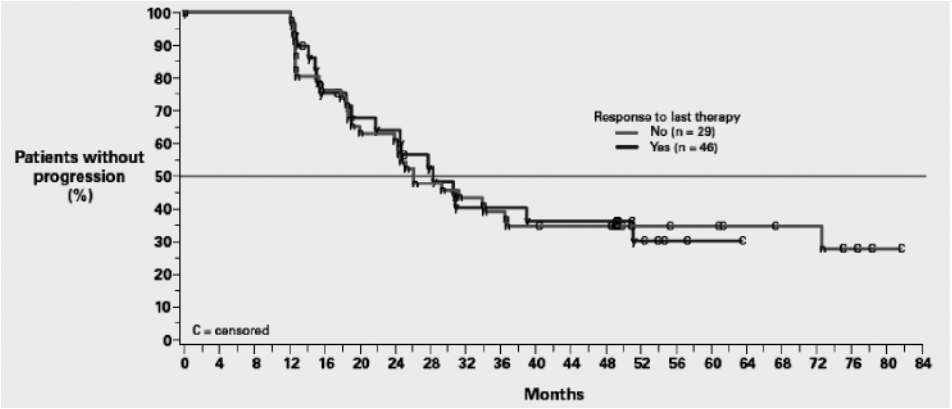

Figure 1. Progression-free Survival of long term responders is independent of response to last regimen.

months, respectively.[8] In patients treated with the maximum tolerated dose of ^{90}Y ibritumomab tiuxetan (0.4 mCi/kg) the median TTP and DR in those with a complete response (CR) were 28.3 months (range, 1.8–75.5+) and 27.5 months (range, 0.7–74.3+), respectively. All patients had been treated previously with chemotherapy, some extensively so, with the median number of prior regimens being 2 (range, 1–7).

Data have shown that using ^{90}Y ibritumomab tiuxetan early in the course of therapy does not preclude the later use of other treatments, such as chemotherapy, immunotherapy, radiotherapy, and autologous stem cell transplantation; nor does its early use have any effect on the potential efficacy of such later treatments.[14-16] However, long term responses exceeding one year of duration were observed also in patients with refractory disease or multiple treatments.

In this report, the characteristics of the cohort of patients with long term responses (TTP ≥12 months) were retrospectively analyzed. The registrational database to assess and compare the safety and efficacy of earlier use of ^{90}Y ibritumomab tiuxetan (at first relapse) and its use later in the course of treatment (after ≥2 prior therapies), since it became apparent that earlier use was associated with longer remissions.

Materials and Methods

Patients and study designs

The data analysis includes patients with relapsed, refractory, or transformed CD20+ B-cell NHL who were treated with ^{90}Y ibritumomab tiuxetan in 4 clinical trials (Table 1). The inclusion criteria were similar in the trials, except for pretreatment platelet count (100,000–149,000/μL in the phase 2 trial in patients with mild thrombocytopenia, ≥100,000/μL in the phase 1-2 dose-finding trial, and ≥150,000/μL in the phase 3 randomized trial that compared ^{90}Y ibritumomab tiuxetan with rituximab and in the phase 3 trial in patients with rituximab-refractory NHL). All patients in the trials had been treated with at least 1 prior therapy for NHL and were rituximab-naive, with the exception of those in the trial that evaluated ^{90}Y ibritumomab tiuxetan in rituximab-refractory disease. All patients were required to have adequate bone marrow reserve, with no more than 25% lymphomatous bone marrow involvement, and an absolute neutrophil count (ANC) of 1500/μL or greater. The exclusion criteria in the trials included prior RIT, prior stem cell transplantation, more than 25% of the bone marrow having received external beam irradiation, central nervous system– or AIDS-related lymphoma, chronic lymphocytic leukemia, and pleural or peritoneal effusions that were cytologically positive for lymphoma. All patients were at least 18 years of age and provided written informed consent, and each participating clinical site received approval from its institutional review board.

Treatment plan and evaluation

Patients were treated with 1 course of the ibritumomab tiuxetan regimen (Figure 1), consisting of an initial infusion of rituximab 250 mg/m^2 followed within 4 hours by an intravenous injection of an imaging dose of 111In ibritumomab tiuxetan 5 mCi on day 1. All patients had normal biodistribution. On day 7, 8, or 9 a second infusion of rituximab 250 mg/m^2 was followed by a weight-based dose of ^{90}Y ibritumomab tiuxetan in an outpatient setting. The dose of ^{90}Y ibritumomab tiuxetan was 0.3 mCi/kg in patients with a pretreatment platelet count of 100,000 to 149,000/μL and 0.4 mCi/kg in those with a count of 150,000/μL or higher. In all cases the maximum total dose was 32 mCi. Doses varied slightly in the phase 1-2 dose-finding trial—3 patients were given rituximab doses of 100 mg/m^2 and 5 patients were given a ^{90}Y ibritumomab tiuxetan dose of 0.2 mCi/kg.[9]

Disease status was evaluated by using medical history, physical examination, bone marrow biopsy, and computed tomography scan or magnetic resonance imaging of the neck, chest, abdomen, and pelvis, as well as other clinically relevant information. These assessments

were repeated every 3 months for the first 2 years and then every 6 months for up to 4 years after treatment. All adverse events (AEs) in the 13 weeks after the first rituximab infusion were recorded, and treatment-related and serious AEs in the 4 years after the first rituximab infusion were recorded. Safety assessments were made from analyses of AEs and clinical laboratory data, using the adult toxicity criteria of the National Cancer Institute's Common Toxicity Criteria, version 2.0. Responses were classified according to the IWRC.[17]

Statistical methods

The objective of the integrated data analysis is to compare key efficacy and safety parameters between patients treated with ^{90}Y ibritumomab tiuxetan after first relapse and those treated with it after more than 2 prior therapies.

The primary efficacy end point in the analysis was the ORR; i.e., CR/CRu rate plus partial response (PR) rate. Other end points were TTP and DR. Time to progression was calculated as the time from the first infusion of rituximab (day 1) to the time of disease progression; DR was calculated as the time from the first observation of a response to the time of disease progression.

Comparison of patients' characteristics between the two groups is based on an analysis of variance for continuous data and a Fisher's exact two-tailed test for categorical data, including the response rates. The Kaplan-Meier method was used in the estimation of time-to-event variables, and the log-rank test was used in the comparison.

Results

Efficacy

A total of 211 patients were treated with ^{90}Y ibritumomab tiuxetan in the 4 clinical trials at 30 US centers between 1996 and 1999. Overall response rates ranged from 73% in the dose finding Phase I/II study to 83% in the phase II study of rituximab-refractory patients; complete response ranged from 15% to 51% iamong various studies. The median duration of response ranged from 6.4 months to 13.9 months acroos the studies.

Characteristics of LTR patients

Of the 211 patients, 78 patients (37%) were identified as long-term responders, according to the definition of having TTP a year or longer, and had a median follow-up of 49.8 months (12.7-81.5+) The median age of the patients was 58 years (24-80). Additional Characteristics are shown on Table 2. Notable a proportion over 30% had tumor size over 5 cm and 37% had refractory disease to their prior regimen. At the time of the analysis the median duration of response was 28.1 months (range 10.5 – 80.3 +months). Median time to progression for LTR was 29.3 months (range 12.1-81.5+ months). Of the long term responders 51 (65%) had achieved complete responses (CR + Cru); in this selected group, median time to progression was 31 months (range 12.1 – 81.5 months). For the patients with ongoing response at the time of the analysismedian time to progression was 53.9 months (range 49-82+ months).

Analysis of patients treated in first line

In the overall group of 211 patients, sixty-three patients (30%) were treated after their first relapse and 148 (70%) after treatment with 2 or more prior therapies. In the latter group, the median number of prior therapies was 3 (range, 2–9), and 36% (53/148) of these patients had been previously treated with 4 or more regimens. Prior therapies consisted of anthracycline-based regimens, single-agent purine analogs, immunotherapy, corticosteroids, and/or other aggres-

Table 1. Summary of trials of 90Y ibritumomab tiuxetan.

Study	*Description*	*Population*	*90Y ibritumomab*	*No. of patients tiuxetan dose (mCi/kg)*
106-03	Phase 1-2 I dose-finding trial	Low- or intermediate-grade or mantle cell NHL	0.2–0.4	51
106-04	Phase 3 randomized trial of ibritumomab tiuxetan regimen vs. rituximab	Low-grade, follicular, or transformed NHL	0.4	73 70*
106-05	Phase 2 trial in patients with mild thrombocytopenia	Low-grade, follicular, or transformed NHL with pretreatment platelet count 100,000–149,000/µL	0.3	30
106-06	Phase 3 trial in patients with rituximab-refractory NHL	Low-grade, follicular, or transformed NHL refractory to rituximab	0.4	57
	Total number of patients treated with and efficacy	^{90}Y ibritumomab tiuxetan and assessed for safety		211

**Patients treated with rituximab only. NHL, non-Hodgkin's lymphoma.*

sive regimens. Patients' characteristics were similar in the groups (Table 3), except that there was a higher rate of lymphomatous marrow involvement in first-relapse patients than in patients with ≥2 prior therapies (57% vs. 39%, p=0.023). There was also a trend toward bulkier disease in patients with ≥2 prior therapies (p=0.08). A high proportion of patients in both groups had NHL with a follicular histology (71% of first-relapse patients and 73% of patients with ≥2 prior therapies). The median age of first-relapse patients was 59 years and of patients with ≥2 prior therapies was 58 years.

As shown in Table 4, the CR/CRu rate was significantly higher in first-relapse patients than in patients with ≥2 prior therapies (49% vs. 28%; p=0.004). The median TTP was also significantly longer in first-relapse patients (12.6 vs. 7.9 months; p=0.025).

In the subpopulation of patients with follicular NHL (n=153) there was a trend toward greater efficacy than in the overall patient population (Table 5). The CR/CRu rates in the follicular NHL population were significantly higher in the 45 first-relapse patients than in the 108 patients with ≥2 prior therapies (51% vs. 28%; p=0.009). In patients with follicular NHL the median TTP was 15.4 months in first-relapse patients and 9.2 months in those with ≥2 prior therapies (p= 0.026).

Table 2. Demographic characteristics of long-term responders LTR.

Median age (range)	58 (24-80)
Gender	
Male	55%
Female	45%
Age > 60 years	44%
Follicular lymphoma	76%
Bone marrow involvement	41%
Bulky disease (> 5cm)	30%
Stage III or IV	83%
Median number of prior therapies (range)	2 (1-9)
1 prior treatment	41%
3 or more prior treatments	33%
No response to last treatment	37%

Table 3. Patient characteristics according to lines of treatment (n=211).

Characteristic	*First-relapse patients (n = 63)*	*Patients with ≥2 prior therapies (n = 148)*	*p*
Age, y, median (range)	59 (24–85)	58 (31–82)	NS
Sex, M/F	32/31	85/63	NS
Stage III or IV disease at study entry	57 (90%)	130 (88%)	NS
Histology		≥	NS
International Working Formulation A	4 (6%)	11 (7%)	
Follicular	45 (71%)	108 (73%)	
Other	14 (22%)	29 (20%)	
Bone marrow involvement	36 (57%)	58 (39%)	0.023
Bulky disease, cm			0.077
<5	34 (54%)	58 (39%)	
5–<7	17 (27%)	38 (26%)	
7–<10	6 (10%)	34 (23%)	
≥10	6 (10%)	18 (12%)	

NS, not significant.

Table 4. Outcomes with ^{90}Y ibritumomab tiuxetan, by number of prior therapies, all patients (n=211).

Outcome	*First-relapse patients (n = 63)*	*Patients with ≥2 prior therapies (n = 148)*	*p*
Overall response, no. (%)	54 (86)	107 (72)	0.051
CR/CRu, no. (%)	31 (49)	42 (28)	0.004
Median TTP, months (range)			
All patients	12.6 (1.2–78.2+)	7.9 (0.8–81.5+)	0.025
Patients with CR/CRu	23.9 (2.7–78.2+)	15.6 (1.8–81.5+)	0.442
Median DR, months (range)			
All patients	13.7 (1.0–77.0+)	8.2 (0.5–80.3+)	0.131
Patients with CR/CRu	22.8 (1.0–77.0+)	14.6 (0.7–80.3+)	0.338

CR, confirmed complete response; CRu, unconfirmed complete response; DR, duration of response; TTP, time to progression.

Table 5. Outcomes with ^{90}Y ibritumomab tiuxetan, by number of prior treatments, patients with follicular lymphoma (n = 153).

Outcome	*First-relapse patients (n = 45)*	*Patients with ≥2 prior therapies (n = 108)*	*p*
Overall response, no. (%)	40 (89)	86 (80)	0.244
CR/CRu, no. (%)	23 (51)	30 (28)	0.009
Median TTP, months (range)	15.4 (2.2–78.2+)	9.2 (1.1–81.5+)	0.026
Median DR, months (range)	16.7 (1.0–77.0+)	8.1 (0.5–81.5+)	0.052

CR, confirmed complete response; CRu, unconfirmed complete response; DR, duration of response; TTP, time to progression.

The median DR in this subpopulation was also longer with earlier administration of ^{90}Y ibritumomab tiuxetan, 16.7 vs. 8.1 months (p= 0.05). In the subpopulation with nonfollicular NHL there was a trend toward a higher ORR for patients treated with ^{90}Y ibritumomab tiuxetan at first relapse (Table 5). CR/CRu rates and time-to-event variables were not significantly increased with earlier therapy in these patients. Moreover, no significant differences in the rates of response were detected among subsets of patients with more aggressive disease histologies based on the timing of RIT (Table 5).

First-relapse patients in the entire study population, as well as those in the follicular NHL subpopulation, had a consistently higher ORR and longer DR than patients with ≥2 prior therapies. In patients with a CR/CRu in the entire population the median DR was 22.8 months in first-relapse patients and 14.6 months in patients with ≥2 prior therapies (p=0.34).

The incidence of grades 3 and 4 hematologic toxicity was similar in first-relapse patients and patients with ≥2 prior therapies (Table 6). The non-hematologic AEs were primarily grade 1 or 2.

Discussion

^{90}Y ibritumomab tiuxetan produces durable response in 37% of the patients who enrolled in the 4 registrational studies with refractory or relapsed B-cell NHL. In some patients the response to treatment continued beyond 6.5 years. The possibility of a durable remission was noted in all groups of patients, including those with bulky disease and multiple lines of treatment. Furhtermore, the documentation of a long term response in patients with refractory disease was remarkable. However, it appears that such a favorable outcome is more likely in patients who received ^{90}Y ibritumomab tiuxetan earlier in their treatment course. The CR/CRu rates are higher and the DRs longer with ^{90}Y ibritumomab tiuxetan when it is used after the first relapse of NHL than when it is used after 2 or more prior therapies. The analysis of the LTR patients indicated that achieving a CR was positively associated with a durable remission.

The benefits of early therapy were particularly notable in patients with follicular NHL, in whom the median TTP was 15.4 months in first-relapse patients, 6.2 months longer than that in those with 2 or more prior therapies. Hematologic toxicity associated with the ^{90}Y ibritumomab tiuxetan therapeutic regimen was acceptable in the indicated population, regardless of whether it was administered at first relapse or later in the course of treatment. However, patients who have been treated with multiple myelosuppressive chemotherapy regimens may not be eligible for subsequent therapy with ^{90}Y ibritumomab tiuxetan because of the requirements for adequate bone marrow reserve, platelet count 100,000/μL or higher, and ANC 1500/μL or higher.

If patients are treated with ^{90}Y ibritumomab tiuxetan early in the course of therapy it is important that subsequent treatment options be preserved. The response rates with subsequent therapy (e.g., single-agent or combination chemotherapy, bioimmunotherapy, and radiotherapy) in 125 patients in whom the disease had relapsed after treatment with ^{90}Y ibritumomab tiuxetan ranged from 47% to 74%, comparable to the rates typically achieved with other agents in later-use settings in relapsed NHL.[18] Furthermore, the hematologic toxicity, transfusion requirements, and hospitalization rates in patients who had been treated with ^{90}Y ibritumomab tiuxetan and subsequent chemotherapy were similar to those in age-, sex-, and histology-matched controls who had been treated with chemotherapy.[15] The incidence of myelodysplastic syndrome did not appear to be greater in patients treated with RIT. This suggests that the tolerability and efficacy of subsequent treatment options are not compromised by earlier treatment with ^{90}Y ibritumomab tiuxetan.

The data on safety and efficacy in this report support the use of ^{90}Y ibritumomab tiuxetan after first relapse, before several courses of chemotherapy, in patients with low-grade and follicular NHL. Yttrium 90 ibritu-

Table 6. Non-hematologic and hematologic toxicities with ^{90}Y ibritumomab tiuxetan, by number of prior therapies.

Grade 3 or 4 toxicities	*No. (%) of patients*			*p*
	All (n = 211)	*First-relapse patients (n = 63)*	*Patients with ≥2 prior therapies (n = 148)*	
Non-hematologic*	44 (21)	12 (19)	32 (22)	NS
Hematologic	159 (75)	51 (81)	108 (73)	NS
Neutropenia	129 (61)	41 (65)	88 (59)	NS
Thrombocytopenia	140 (66)	43 (68)	97 (66)	NS
Anemia	39 (18)	8 (13)	31 (21)	NS

**The most common grade 3 or 4 non-hematologic toxicities were infection, asthenia, abdominal pain, and dyspnea. All of which occurred in < 5% of the study population. NS, not significant.*

momab tiuxetan appears to produce response rates and DRs comparable to those achieved with most chemotherapy regimens used in patients with relapsed or refractory NHL, without the frequency or severity of the nonhematologic AEs that occur with chemotherapy. Early use of ^{90}Y ibritumomab tiuxetan induces higher and longer remissions, even among patients with adverse characteristics, and such a use should be considered when selecting a therapy for relapsed or refractory indolent B-cell lymphoma. Use of ^{90}Y ibritumomab tiuxetan can safely and productively be combined with chemotherapy[19] In fact the feasibility and safety of early introduction of ^{90}Y ibritumomab tiuxetan in the treatment course promoted the design of prospective studies evaluating frontline ^{90}Y ibritumomab tiuxetan, either as a single agent or as a consolidation therapy, in follicular lymphoma.[20,21]

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