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Radioimmunotherapy for patients with relapsed B-cell non-Hodgkin lymphoma

Abstract Clinical trials of an yttrium-90 (^{90}Y)-conjugated monoclonal antibody to CD20 in patients with relapsed B cell non-Hodgkin lymphoma (NHL) are reviewed. Ibritumomab is the murine parent anti-CD20 antibody engineered to make the human chimeric antibody rituximab. Tiuxetan is an MX-DTPA linker chelator attached to ibritumomab to form ibritumomab tiuxetan (Zevalin). Ibritumomab tiuxetan can react with indium-111 (^{111}In) or ^{90}Y to form ^{111}In-ibritumomab tiuxetan, which is used for dosimetry, or ^{90}Y-ibritumomab tiuxetan, which is used for therapy of B cell NHL. In this report, the results of five separate clinical trials of ibritumomab tiuxetan are reviewed. Two phase I trials of ^{90}Y-ibritumomab tiuxetan were performed, one using cold ibritumomab prior to ^{90}Y-ibritumomab tiuxetan, and one using rituximab prior to ^{90}Y-ibritumomab tiuxetan. The optimal schedule was found to be rituximab on days 1 and 8, and ^{90}Y-ibritumomab tiuxetan 0.4 mCi/kg i.v. on day 8; no stem cells or prophylactic growth factors were used. A dose of 0.3 mCi/kg was recommended for patients with a baseline platelet count of 100,000–149,000×10^6/l. The only significant toxicity was reversible myelosuppression. With this schedule, the overall response rate (ORR) was 67% of all patients and 82% of those with low-grade NHL. The phase I/II trials were followed by a phase III trial that randomized 143 eligible patients to either rituximab or ^{90}Y-ibritumomab tiuxetan radioimmunoconjugate to demonstrate that the combination of the ^{90}Y radioisotope to the murine anti-CD20 antibody provided additional efficacy over the unconjugated (“cold”) rituximab alone. A planned interim analysis of the first 90 patients demonstrated an ORR of 80% with ^{90}Y-ibritumomab tiuxetan vs 44% for rituximab ($P < 0.05$). To provide additional evidence of the benefit of ^{90}Y radioimmunotherapy over rituximab immunotherapy, patients who were nonresponsive or refractory to rituximab were enrolled in an additional trial and treated with ^{90}Y-ibritumomab tiuxetan 0.4 mCi/kg. An ORR of 46% was achieved in these rituximab-refractory patients. These results provide further evidence of the added value of ^{90}Y. Therefore ^{90}Y-ibritumomab tiuxetan radioimmunotherapy is a useful new treatment modality for patients with B cell NHL. Future trials are needed to define the optimal time in the disease course when this modality should be used.

Keywords Non-Hodgkin lymphoma · Radioimmunotherapy · Monoclonal antibody · CD20

Introduction

The most important therapeutic advance in the treatment of B cell non-Hodgkin lymphoma (NHL) that has occurred in the past few years is the development of targeted immunotherapy. There are several possible targets on the B lymphocyte. The CD20 antigen is expressed in nearly all B cell NHL and is absent from other nonlymphoid cells, making it an ideal target for immunotherapy. Rituximab (Rituxan and MabThera; IDEC Pharmaceuticals Corporation, San Diego, Calif., and Genentech, South San Francisco, Calif., respectively) is a chimeric monoclonal antibody (mAb) that reacts with the CD20 cell surface antigen. Rituximab was the first mAb approved by the US Food and Drug Administration for use in treating malignancy and the first drug approved for low-grade NHL. The mechanism of action of rituximab is not entirely understood; however, in vitro experiments have demonstrated induction of apoptosis

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in target cells and antibody-dependent cellular cytotoxicity (ADCC) [13]. In the largest clinical trial to date rituximab was studied in 166 patients with relapsed B cell NHL and an overall response rate (ORR) of 48% was found, with 6% achieving complete remission (CR) and a 13-month time to progression (TTP) [14].

There is a need to improve those results with rituximab, and several approaches are being attempted. First, neither the actual maximum tolerated (or effective) dose nor the total number of doses of rituximab have been determined since the original studies were limited by drug supply. Thus it will be interesting to learn whether trials utilizing doses >375 mg/m^2 or courses of therapy that provide more than four weekly doses of rituximab can improve the ORR and TTP. Second, rituximab has been shown to be safe when combined with chemotherapy because it is not usually myelosuppressive [1]. Several large cooperative group trials currently underway in Europe and the USA are addressing the efficacy of chemotherapy plus rituximab in new or relapsed low- or intermediate-grade NHL. The results of these trials will have a major impact on future use of combined immuno- and chemotherapy.

Third, since rituximab works through ADCC, it is possible that a higher response rate would be achieved if cellular immunity could be enhanced. This has led to phase I studies combining rituximab and interleukin-12 at our institution. Fourth, the efficacy of mAbs could be improved if the antibody were utilized to target radiation or toxins to the tumor cell. Kreitman et al. have recently demonstrated excellent results in patients with relapsed lymphoproliferative tumors expressing CD25 [11]. They used an anti-CD25 antibody conjugated to *Pseudomonas* exotoxin. The most commonly used radionuclides linked to murine mAbs are iodine-131 (^{131}I) [2, 6, 9, 12, 17], yttrium-90 (^{90}Y) [10, 23], and copper-67 (^{67}Cu) [3]. In radioimmunotherapy (RIT) the mAb is primarily utilized to focus the radiation on the target cell population while sparing nearby healthy tissue. Recent studies of RIT have demonstrated tumor regressions in patients with NHL with few side effects in normal organs other than myelosuppression due to bone marrow irradiation [2, 3, 6, 7, 8, 9, 10, 12, 15, 16, 23].

Clinical trials with radiolabeled ibritumomab tiuxetan

Ibritumomab is the murine mAb engineered to form the chimeric antibody rituximab. Tiuxetan is an MX-DTPA linker chelator attached to ibritumomab to form ibritumomab tiuxetan (Zevalin). Ibritumomab tiuxetan is subsequently reacted with indium-111 (^{111}In) or ^{90}Y to form ^{111}In-ibritumomab tiuxetan, which is used for dosimetry, or ^{90}Y-ibritumomab tiuxetan, which is used for therapy. Five trials of ^{90}Y-ibritumomab tiuxetan have recently been completed (Table 1) [4, 10, 21, 22, 23]. In the first study by Knox et al. [10], cold ibritumomab was used prior to each dose of ^{90}Y-ibritumomab tiuxetan. A group of 18 patients were treated in this study with doses of ^{90}Y-ibritumomab tiuxetan 13.5–50 mCi. The ORR was 72% (13 of 18) with 33% (6 of 18) achieving CR. Doses ≤ 40 mCi were found to be nonmyeloablative.

The next study was a phase I/II trial of ^{90}Y-ibritumomab tiuxetan to determine the rituximab (instead of cold ibritumomab) dose necessary for optimal ^{111}In-ibritumomab tiuxetan dosimetry and to establish the maximum tolerated dose of ^{90}Y-ibritumomab tiuxetan without the use of stem cells or prophylactic growth factors [23]. Rituximab was administered before each ibritumomab tiuxetan dose to bind to nonspecific CD20 antigenic sites and to deplete normal blood B cells, allowing the infused ibritumomab tiuxetan more opportunity to bind to CD20 sites on malignant cells. In the previous phase I trial, it was found that 250 mg/m^2 was the optimal rituximab dose before ^{111}In-ibritumomab tiuxetan imaging and ^{90}Y-ibritumomab tiuxetan therapy. Dosimetry predicted that all patients were eligible for ^{90}Y-ibritumomab tiuxetan; i.e. all normal nontumor-bearing organs were predicted to receive <2000 Gy and bone marrow <300 cGy. The median age was 60 years and 24% of the 12 patients were >70 years of age. The tumor histology was low-grade in 66%, intermediate-grade in 28%, and mantle cell lymphoma in 6%. In the low-grade group, 6% had diffuse small lymphocytic, 27% follicular small cleaved, and 33% follicular mixed lymphoma. All patients had received prior chemotherapy (median of two prior regimens), and 92% had

Table 1 Recently completed trials of ^{90}Y-ibritumomab tiuxetan

Trial	Phase	Goal	Reference
IDEC 106-02	I	Used cold ibritumomab prior to ^{90}Y-ibritumomab tiuxetan; determine maximum tolerated dose of ^{90}Y-ibritumomab tiuxetan	*10*
IDEC 106-03	I/II	Determine dose of rituximab prior to ^{111}In-ibritumomab tiuxetan; determine maximum tolerated dose of ^{90}Y-ibritumomab tiuxetan	*23*
IDEC 106-04	III	Randomized trial of rituximab vs ^{90}Y-ibritumomab tiuxetan to determine if efficacy of ^{90}Y-ibritumomab tiuxetan is superior	*21*
IDEC 106-05	II	Efficacy and toxicity of ^{90}Y-ibritumomab tiuxetan 0.3 mCi/kg for patients with platelet count 100,000–149,000$\times 10^6$/l	*22*
IDEC 106-06	II	Efficacy and toxicity of ^{90}Y-ibritumomab tiuxetan 0.4 mCi/kg in rituximab-refractory patients	*4*, *18*

received an anthracycline. Prior external beam radiotherapy had been used in 37%; 27% had two or more extranodal sites of disease, 59% had bulky disease (defined as a mass ≥5 cm), and 43% had positive bone marrow. Five patients received ^{90}Y-ibritumomab tiuxetan 0.2 mCi/kg, 15 received 0.3 mCi/kg, and 30 received 0.4 mCi/kg in the phase I/II trial. It was found that 0.4 mCi/kg was the maximum tolerated single dose that could be delivered without the use of stem cells or prophylactic growth factors.

The efficacy portion of the phase I/II trial (Table 2) demonstrated a 67% ORR in all patients, with 26% achieving CR. In patients with low-grade NHL, the ORR was 82%, with 26% achieving CR [23]. The median TTP for responders was 15.4 months.

Based on the results of these phase I/II studies, three additional trials were performed using ^{90}Y-ibritumomab tiuxetan RIT delivered over an 8-day period on an outpatient basis. In each study, patients received rituximab 250 mg/m^2 on day 1, followed by ^{111}In-ibritumomab tiuxetan 5.5 mCi. Between day 1 and day 7, whole-body scans were performed to predict the amount of radiation the tumor and healthy organs would receive when ^{90}Y-ibritumomab tiuxetan was administered. The study protocols allowed ^{90}Y-ibritumomab tiuxetan to be administered on day 8 if the predicted dose to healthy organs was <2000 cGy and <300 cGy to the bone marrow. The ^{111}In images also provided evidence that the radioimmunoconjugate was targeting known tumor sites. The dosimetry results are summarized elsewhere [19, 20].

Table 2 Response rates (%) to ^{90}Y-ibritumomab tiuxetan in patients in IDEC 106-03 [23]. These results include all patients treated with doses 0.2, 0.3, and 0.4 mCi/kg

Histology (*n*)	Overall response rate	Complete remission	Partial remission
All patients (51)	67	26	41
Low grade (34)	82	26	56
Intermediate (14)	43	29	14
Mantle cell (3)	0	0	0

Table 3 Interim analysis of response to therapy in the first 90 patients accrued in the randomized trial of ^{90}Y-ibritumomab tiuxetan vs rituximab (IDEC trial 106-04) [21] (*95%CI* 95% confidence interval)

Response rate	Rituximab (%) (95%CI)	^{90}Y-ibritumomab tiuxetan (%) (95%CI)	*P*-value
Overall	44 (28.1–58.9)	80 (64.2–89.7)	<0.001
Complete	7	21	0.06
Partial	37	59	

The results of the phase I/II trial [23] suggested that there is a higher ORR to ^{90}Y-ibritumomab tiuxetan than that reported for rituximab [14]. However, it was necessary to confirm this in a prospective, randomized trial of ^{90}Y-ibritumomab tiuxetan vs rituximab. Patients with relapsed CD20$^+$ NHL were randomized to receive either ibritumomab tiuxetan 0.4 mCi/kg (maximum 32 mCi) or rituximab 375 mg/kg weekly ×4 [21]. Patients were eligible for this trial if they had biopsy-proven low-grade, follicular or transformed NHL, ECOG performance status of 0–2, absolute neutrophil count of $\geq 1500\times10^6$/l, and platelet count $\geq 150{,}000\times10^6$/l. A pretreatment bone marrow analysis was performed and was required to show $<25\%$ of the marrow cellularity occupied by NHL. Prior external beam radiation therapy must have included $<25\%$ of the bone marrow. Patients could not have received prior anti-CD20 antibody therapy, recent colony-stimulating factors, or high-dose chemotherapy with stem cell rescue. Patients were also ineligible if they had human anti-mouse or anti-chimeric antibody (HAMA/HACA) or ≥5000 μl tumor cells circulating in the blood. Patients with NHL related to the human immunodeficiency virus or those with chronic lymphocytic leukemia or central nervous system NHL were also ineligible.

A total of 143 patients were randomized in IDEC 106-04 and the trial was closed in August 1999 after reaching accrual goals. A planned single interim analysis was performed after 90 patients had been enrolled and treated, and the preliminary results are available for this group [21]. The patients were stratified by histologic subtype (small lymphocytic, follicular, and transformed) to ensure balance in the two treatment arms. The interim analysis showed an ORR of 80% with ^{90}Y-ibritumomab tiuxetan compared with 44% for rituximab ($P<0.05$). The CR rate of 21% in the ^{90}Y-ibritumomab tiuxetan arm was also higher than the 7% in the rituximab arm ($P=0.06$) (Table 3).

Table 4 Bone marrow toxicity experienced in four clinical trials of ^{90}Y-ibritumomab tiuxetan (*NA* not applicable)

IDEC study	Absolute neutrophil nadir			Platelet count		
	Nadir ($\times10^6$/l)	% Grade 4 ($<500\times10^6$/l)[a]	Median duration (days)	Nadir ($\times10^6$/l)	% Grade 4 ($<10{,}000\times10^6$/l)[b]	Median duration (days)
103 [23]	1100	27	10.5	49,500	10	14
104 [21]	900	25	14	42,000	6	12
105 [22]	600	25	NA	34,000	15	NA
106 [4]	900	23	14	34,000	8	15

[a]Grade 4 neutropenia $<500\times10^6$/l
[b]Grade 4 thrombocytopenia $<10{,}000\times10^6$/l

Data from the additional 53 patients and longer follow-up are necessary to determine whether there are differences between treatment arms in time to next chemotherapy or overall survival. Although there were few patients with the diffuse small lymphocytic histologic subtype, the response to ibritumomab tiuxetan was superior at 80% vs 17% to rituximab. In addition, the ORR to ibritumomab tiuxetan in the chemotherapy-resistant group was 77% compared with 32% to rituximab [24].

In this trial, ^{111}In-ibritumomab tiuxetan was used for dosimetry in patients randomized to ibritumomab tiuxetan. The biodistribution and dosimetry were acceptable in all cases. Therefore no patient was unable to receive the therapeutic dose. The calculated ibritumomab tiuxetan half-lives and bone marrow dosimetry-estimated absorbed radiation doses did not correlate with hematologic toxicity. Patient tolerance of both ibritumomab tiuxetan and rituximab was excellent, and there were no significant major organ toxicities except for transient, reversible hematologic toxicity in patients who received ibritumomab tiuxetan (Table 4). The median nadir platelet count was $42{,}000\times10^6$/l, median absolute neutrophil count 900×10^6/l, and median hemoglobin 10.9 g/dl. Only 6% of patients developed grade 4 thrombocytopenia (defined in this study as $<25{,}000\times10^6$/l) and 25% developed grade 4 neutropenia ($<500\times10^6$/l). Patients who developed grade 3 or 4 thrombocytopenia or neutropenia recovered in a median of 12 and 14 days, respectively. Infection or hypogammaglobulinemia was uncommon [5]. Only one patient in each arm of the protocol has developed HAMA or HACA to date.

The finding that bone marrow suppression was the main toxicity with administration of ^{90}Y-ibritumomab tiuxetan 0.4 mCi/kg led to a separate clinical trial of reduced-dose ^{90}Y-ibritumomab tiuxetan (0.3 mCi/kg) for patients with platelet counts $100{,}000$–$149{,}000\times10^6$/l [22]. A total of 30 patients were enrolled in this study, which closed in August 1999 after meeting targeted accrual. The results of the interim analysis of the first 24 patients have been reported [22]. The median age of the 30 patients was 61 years, and 25% were ≥75 years old. The tumor histology was follicular in 83%, diffuse small lymphocytic subtype in 4%, and 14% had transformed from a low- to an intermediate-grade NHL. All patients had relapsed disease after receiving chemotherapy. Biodistribution of ^{90}Y-ibritumomab tiuxetan was measured by ^{111}In-ibritumomab tiuxetan scans, and all patients met the dosimetry criteria to receive ^{90}Y-ibritumomab tiuxetan. As expected, the main toxicity was hematologic. The median nadir absolute neutrophil count was 600×10^6/l and reached grade 4 in 25% of patients. The median platelet count was $34{,}000\times10^6$/l, and 15% of the patients experienced grade 4 thrombocytopenia. The ORR was 68%, with 23% of patients achieving CR and 45% partial remission (PR). The duration of response and TTP have not yet been analyzed.

Since the response rate to cold rituximab is approximately 50% and the duration of response about 1 year, a large group of patients fail rituximab at some point. The goal of IDEC study 106-06 was to determine whether patients who had failed to respond to rituximab with a PR or CR or had a response of <6 months duration would respond to RIT with ^{90}Y-ibritumomab tiuxetan. An interim analysis of the first 26 patients has been reported [4]. The median age of the treated population was 56 years, 92% had tumors with follicular histology, and patients had received a median of three prior regimens. Of the patients 46% had bulky disease (defined as >7 cm) and 27% bone marrow involvement. The dosimetry determined by ^{111}In-ibritumomab tiuxetan was acceptable in all cases. The nadir absolute neutrophil count was 900×10^6/l and in 23% of patients reached grade 4. The nadir platelet count was $34{,}000\times10^6$/l and was grade 4 in 8%. The ORR was 46%, indicating that the addition of ^{90}Y was beneficial.

The interim analysis of the randomized, controlled trial of rituximab vs ^{90}Y-ibritumomab tiuxetan [21] and the ability of ^{90}Y-ibritumomab tiuxetan to produce responses in patients who had failed rituximab [4] provide evidence that the addition of a radioactive particle to the mAb improves the response rate when compared with that achieved with the same mAb without ^{90}Y. The only significant toxicity associated with ^{90}Y-ibritumomab tiuxetan was hematologic and it was reversible. The rare development of HAMA/HACA indicates that retreatment with ^{90}Y-ibritumomab tiuxetan may be feasible, although this remains to be investigated. The lack of correlation between the special dosimetry performed in this trial and hematologic toxicity indicates that it may be optional in future trials of ^{90}Y-ibritumomab tiuxetan.

Conclusion

Some important information on ^{90}Y-ibritumomab tiuxetan RIT has been obtained. Future clinical trials are necessary to determine whether multiple doses of ^{90}Y-ibritumomab tiuxetan can be provided to increase the CR rate and prolong TTP. In addition, trials to integrate RIT with chemotherapy with or without stem cell support are required to confirm that these combinations can be administered safely and whether the cure rate can be improved.

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