

Radioimmunotherapy for B-Cell Non-Hodgkin Lymphoma

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Abstract: Radioimmunotherapy is an established and effective treatment in B-cell non-Hodgkin lymphoma (NHL). Currently, two radioimmunoconjugates (RICs) are approved for clinical use in the United States, ibritumomab tiuxetan and tositumomab. Both agents target the CD20 antigen on B-cell lymphoma cells. Although there are differences between these two agents, such as different murine monoclonal antibodies, radioisotopes, and dosimetry techniques, they share similar toxicity and efficacy profiles. These anti-CD20 RICs are active in patients who are refractory to single-agent rituximab, documenting the added value of the conjugated radioisotope. This review focuses on the current use of these agents in the treatment of previously untreated indolent NHL and relapsed/refractory and transformed NHL.

In the last decade, immunotherapy has become an important component of the treatment of B-cell non-Hodgkin lymphomas (NHL). Rituximab (Rituxan, Genentech/Biogen Idec) was the first monoclonal antibody to be approved by the US Food and Drug Administration (FDA) for the treatment of lymphoma, based on its single-agent activity in relapsed B-cell NHL.¹ Since its introduction, considerable effort was focused on the improvement of rituximab efficiency. One approach, to combine rituximab with chemotherapy, was demonstrated to be effective in a number of clinical trials.²⁻⁴ Another approach to enhance the efficiency of immunotherapy was to improve the antibodies themselves. The increase in killing potential of the antibodies can be achieved by linking them to a toxin (immunotoxin) or a radionuclide (radioimmunoconjugate [RIC]). The latter approach, referred as to radioimmunotherapy (RIT), has the advantage of targeting not only the cell to which the antibody is bound, but also the surrounding tumor cells and microenvironment. The RIC kills tumor cells by the direct effects of the antibody, such as antibody-dependent cellular cytotoxicity (ADCC), as well as by the effects of the ionizing radiation. There is also evidence that antibodies binding to CD20 molecules can enhance the proapoptotic effects of radiation.⁵ This review focuses on RIT that targets CD20, since it is now in clinical use for FDA-approved indications.⁶

Keywords

Radioimmunotherapy, NHL, ibritumomab tiuxetan, tositumomab, CD20.

Anti-CD20 Radiolabeled Antibodies

Currently, there are two RICs registered in the US, ibritumomab tiuxetan (Zevalin, Biogen Idec) and tositumomab (Bexxar, GlaxoSmithKline).

Ibritumomab Tiuxetan

Ibritumomab, a murine anti-CD20 antibody, was attached to tiuxetan, a methylbenzyl diethylene-triaminepentaacetic acid linker-chelator, to form the compound ibritumomab tiuxetan. Tiuxetan forms a covalent, urea-type bond with ibritumomab and chelates the radionuclide via five carboxyl groups. Ibritumomab tiuxetan is then coupled with either indium-111 (^{111}In) for tumor imaging and dosimetry or with yttrium-90 (^{90}Y) for therapy. ^{90}Y emits pure beta radioactivity with a path length of approximately 5 mm. Since there is no gamma emission, tumor and normal organ images cannot be obtained with ^{90}Y -ibritumomab tiuxetan. Therefore, gamma-emitting ^{111}In -ibritumomab tiuxetan is used to produce images of the tumor and normal organs for dosimetry and biodistribution studies.⁷ The images are usually obtained between days 1 and 7 following ^{111}In -ibritumomab tiuxetan injection to ensure that the ^{90}Y -ibritumomab tiuxetan is targeting the tumor and that no unusual pattern of biodistribution to normal organs is occurring. The FDA currently requires one ^{111}In -ibritumomab tiuxetan image 48 hours after injection (a second image is optional) for routine applications. This image is used to check for normal biodistribution but is not used to calculate the dose of ^{90}Y -ibritumomab tiuxetan. Rather, the dose of ^{90}Y -ibritumomab tiuxetan is determined by weight and baseline platelet count. The unlabeled antibody (rituximab 250 mg/m²) is given before ^{90}Y -ibritumomab tiuxetan to improve biodistribution.⁸ If there is normal biodistribution, on day 8 the patient receives another dose of rituximab followed by ^{90}Y -ibritumomab tiuxetan. If the platelet count is normal (>150,000 cells/ μL) the recommended dose is 0.4 mCi/kg; if the platelet count is between 100,000–150,000 cells/ μL the dose is 0.3 mCi/kg. The dose is capped at 32 mCi for patients weighing 80 kg and over.

Tositumomab

Tositumomab is a murine monoclonal antibody that binds to CD20. For RIT, tositumomab is radiolabeled with iodine-131 (^{131}I). Since ^{131}I emits gamma as well as beta radiation, it can be used for both dosimetry and treatment.⁹ In contrast to ^{90}Y -ibritumomab tiuxetan, the therapeutic dose of tositumomab is based on dosimetry.¹⁰ Patient-specific dosing is necessary because of interpatient differences in spleen size, tumor burden, and ^{131}I metabolism and renal excretion.^{9–13} Iodine concentrate (Lugol's solution) is given before treatment to block ^{131}I uptake in the thyroid. On day 1, a dose of 450 mg of cold (unlabeled) tositumomab fol-

lowed by 5 mCi of ^{131}I - tositumomab is given. Dosimetry is performed on day 1 and repeated within 2–4 days and 6–7 days after the dose. Patients receive a dose of ^{131}I -tositumomab calculated to deliver 75 cGy to the whole body for patients who have a platelet count over 150,000 cells/ μL or a dose of 65 cGy for patients with platelets between 100,000 and 150,000 cells/ μL . The therapeutic dose is given within 7–14 days of the dosimetric dose and consists of 450 mg of cold tositumomab followed by the calculated dose of ^{131}I -tositumomab.

Phase I Studies and Toxicity of Anti-CD20 Radioimmunoconjugates

Phase I studies of ^{90}Y -ibritumomab tiuxetan and ^{131}I -tositumomab not only identified the toxicities and maximum tolerated dose, but also established the role of predosing with cold anti-CD20 antibodies to improve biodistribution of the RIC. The phase I study of ^{90}Y -ibritumomab enrolled patients with relapsed low- or intermediate-grade CD20(+) B-cell NHL.¹⁴ Comparison of images with ^{111}In -ibritumomab tiuxetan performed with and without predosing with unlabeled ibritumomab revealed that predosing with cold antibodies improved biodistribution of ^{111}In -ibritumomab tiuxetan. The second phase I study tested predosing with rituximab rather than cold ibritumomab, since rituximab (a humanized antibody, in contrast to murine ibritumomab) was less likely to induce the formation of human antimurine antibodies (HAMA) against ibritumomab tiuxetan. Fifty-one patients with low- and intermediate-grade or mantle cell lymphoma were enrolled. The study concluded that 250 mg/m² was the optimal dose of rituximab to be used before ^{111}In -ibritumomab tiuxetan imaging and ^{90}Y -ibritumomab tiuxetan therapy,⁸ although doses higher than 250 mg/m² were not tested. The doses of ^{90}Y -ibritumomab tiuxetan used in the phase I/II trial were 0.2, 0.3, and 0.4 mCi/kg. The dose was not increased above 0.4 mCi/kg because substantial myelosuppression was already being observed at the 0.4-mCi/kg dose and the goal was to develop a regimen that did not require stem cell support. The efficacy portion of the phase I/II trial demonstrated a 67% overall response rate (ORR) with 26% of patients achieving a complete response (CR).⁸

In the phase I trial of ^{131}I -tositumomab, the therapeutic dose was established as 75 cGy. Predosing with 450 mg of cold tositumomab produced optimal tumor/normal organ biodistribution.^{11,15,16} The ORR was 71% (42/59) with a CR rate of 34% (20/59). The patients with low-grade or transformed NHL had an ORR of 83% compared to 41% in those with intermediate-grade NHL.¹⁶

Safety data from the above-mentioned phase I studies and subsequent efficacy studies showed that the primary toxicity of RIT is myelosuppression, which is dose-limit-

ing if stem cell support is not used.^{17,18} The hematologic nadir occurs at 6–9 weeks following a single dose of RIT and lasts approximately 2 weeks. Interestingly, despite neutropenia, infections are unusual, possibly due to the lack of mucosal damage from RIT. Other toxicities are usually mild. The incidence of HAMA is less than 2% with ibritumomab tiuxetan and approximately 10% with tositumomab. However, the latter agent as a first-line therapy was associated with the development of HAMA in 63% of patients (see below). Development of myelodysplasia and acute leukemia has been observed in patients treated with RIT; however, these patients had been treated with chemotherapy that included alkylating agents and/or purine nucleoside analogs prior to RIT.¹⁷⁻¹⁹ In the study of previously untreated patients who received RIT, to date none of the patients has developed myelodysplasia.²⁰ However, longer follow-up will be necessary to fully elucidate the risk of myelodysplasia with RIT.

Radioimmunotherapy in Indolent Lymphoma

The largest experience with RIT has been accumulated for indolent lymphomas. It should be cautioned that results of the studies are applicable to the populations previously studied (eg, <25% bone marrow involvement by lymphoma, absolute neutrophil count $\geq 1,500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, normal renal and liver function, and <25% of the bone marrow previously treated with external beam radiotherapy).

Previously Untreated Patients

A phase II study by Kaminski and colleagues²⁰ of ¹³¹I-tositumomab in previously untreated patients with follicular lymphoma showed high efficacy with this treatment. The study enrolled 76 patients with previously untreated advanced-stage (stage 3 or 4) follicular lymphoma (71% and 29% follicular grades 1 and 2, respectively). Sixty-three percent of the patients had bone marrow involvement, 31% had an elevated lactate dehydrogenase (LDH) level, and 43% had bulky disease (masses ≥ 5 cm). The patients' median age was 49 years (range, 23–69). The ORR was 95% (72/76) with a CR rate of 74% (56/76). Molecular CR was seen in 80% of assessable patients. After a median follow-up of 5.1 years, the 5-year progression-free survival for all patients was 59%. As expected, the main toxicity was moderate myelosuppression and no patient required a transfusion or use of growth factor. Seven percent of the patients developed hypothyroidism and have subsequently required oral thyroid supplementation. Interestingly, 63% of patients developed HAMA, a considerably higher percentage than observed in previously treated patients.^{11,19,21} The mechanism behind this difference is likely to be related to the immunosuppression from chemotherapy in previously treated patients.

Studies evaluating combinations of up-front chemotherapy followed by consolidation with RIT are ongoing. The rationale for these studies is to provide initial tumor debulking with chemoimmunotherapy prior to RIT, with the aim of increasing its effectiveness. In addition, chemotherapy can decrease bone marrow involvement by NHL, allowing the treatment of patients otherwise ineligible for RIT due to extensive bone marrow involvement. The long-term benefits of this approach remain unclear at this point and further randomized studies will be necessary.

Patients With Relapsed and Refractory Disease

Studies in relapsed and refractory follicular NHL were the first clinical studies of efficacy performed using RIT, and a large body of literature exists. This review focuses on a few pivotal studies. A phase II study by Vose and coauthors²¹ enrolled 47 patients with relapsed low-grade or transformed NHL. Patients received either 75 or 65 cGy of ¹³¹I-tositumomab depending on baseline platelet count. Patients' median age was 49 years (range, 23–74). The histology was low-grade in 79% and transformed in 21% of patients. The patients had received a median of four prior chemotherapy regimens (range, 1–8), LDH level was elevated in 38%, and bone marrow was involved in 51%. The ORR was 57%, and 32% of patients obtained a CR. The median response duration was 9.9 months. The achievement of CR was associated with a median response duration of 19.9 months. The median overall survival from study entry was 36 months, with no deaths due to the treatment.

The efficacy of ¹³¹I-tositumomab was compared to that achieved by the patients' last qualifying chemotherapy in a study by Kaminski and coworkers.¹⁹ The study enrolled 60 patients with relapsed low-grade (n=36), transformed (n=23), or mantle cell (n=1) NHL. The patients had received a median of four prior chemotherapy regimens (range, 2–13) and were required to have failed to respond or to have progressed within 6 months of the last chemotherapy regimen. Forty-four percent of the patients had an elevated LDH level and 55% had bulky disease (mass ≥ 5 cm). The median response duration with ¹³¹I-tositumomab was 6.5 months, compared to 3.4 months with chemotherapy. The ORR was 65% with ¹³¹I-tositumomab, compared to 28% with chemotherapy ($P<.001$). Seventeen percent of patients had a CR with ¹³¹I-tositumomab compared to 3% with chemotherapy ($P=.01$). The ORR with ¹³¹I-tositumomab differed between the low-grade and transformed patient groups: 81% of the low-grade patients had a tumor response, compared to 39% (9/29) of the patients with transformed NHL.¹⁹

¹³¹I-tositumomab has also been compared with cold tositumomab.²² Seventy-eight patients with relapsed low-grade or transformed NHL were randomized to receive ¹³¹I-tositumomab or two doses of cold tositumomab. The

patients' median age was 55 years (range, 28–85), and they had received a median of two prior regimens (range, 1–5). Eighty-eight percent of patients had stage III/IV disease; 40% had elevated LDH levels; and 41% had bulky disease (≥ 5 cm). The ORR was 67% (28/42) for ^{131}I -tositumomab compared to 28% for those who received cold tositumomab ($P < .001$). The response duration was 18 months for tositumomab, and it had not been reached at the time the study was reported for ^{131}I -tositumomab. Crossover was allowed and 19% of patients crossed over to the ^{131}I -tositumomab arm after progression. Of these, 89% responded with 42% CR. Thirteen patients did not cross over, including 8 patients who developed HAMA.

^{90}Y -ibritumomab tiuxetan was compared to rituximab in patients with relapsed CD20(+) NHL who had never received rituximab. Patients were randomized to receive either 0.4 mCi/kg (maximum of 32 mCi) ^{90}Y -ibritumomab tiuxetan or rituximab 375 mg/kg weekly for four doses.²³ One hundred forty-three patients were randomized (73 and 70 received ^{90}Y -ibritumomab tiuxetan and rituximab, respectively). The patients were stratified by histologic subtypes (small lymphocytic, follicular, and transformed). The ORR (according to International Workshop NHL criteria²⁴) was 80% with ^{90}Y -ibritumomab tiuxetan, compared to 56% for rituximab ($P = .002$). The CR rate was 30% in the ^{90}Y -ibritumomab tiuxetan group and 16% in the rituximab group ($P = .04$). The estimated median time to progression (TTP) was similar in both groups: 11.2 months or more (range, 0.8–31.5+) for the ^{90}Y -ibritumomab tiuxetan group and 10.1 months or more (range, 0.7–26.1) for the rituximab group ($P = .173$). However, the estimated time to next therapy for patients with nontransformed histology was significantly longer for ^{90}Y -ibritumomab tiuxetan patients (17.8+ mo; range, 2.1–21.7+) than for rituximab patients (11.2 mo; range, 1.3–19.0+; $P = .040$).

Since most patients with low-grade B-cell NHL receive rituximab early in the disease course, the efficacy of RIT in patients failing treatment with rituximab is particularly relevant. Horning and colleagues²⁵ evaluated ^{131}I -tositumomab therapy in 38 patients who had relapsed after receiving rituximab. The patients' median age was 57 years, 68% had received at least four prior chemotherapy regimens, and 32% had bone marrow involvement. Of the 38 patients treated, 33 were evaluable for the response. The ORR was 58%, and the CR rate was 21%. The ORR did not significantly differ for the 24 patients who were refractory to rituximab (ORR = 57%) compared with the 12 patients who had a response to rituximab that lasted less than 6 months (ORR = 55%). Activity of ^{90}Y -ibritumomab tiuxetan in rituximab-refractory patients has also been tested.²⁶ The median age was 54 years (range,

34–73), 95% of patients had follicular NHL, 32% had bone marrow involvement, and 74% had bulky disease (≥ 5 cm). This patient group was heavily pretreated with a median of four prior therapies. The ORR using International Workshop criteria²⁴ was 74%, with a CR rate of 15%. The median estimated TTP was 6.8 months (range, 1.1–25.9+).

In summary, RIT produces an ORR of approximately 60–80% and a CR in 15–30% of patients with relapsed/refractory low-grade B-cell NHL (Figure 1). RIC produces a higher response rate than the respective cold unlabeled antibody. RIT has a high response rate (approximately 75–80%) in rituximab-refractory patients.

Transformed NHL

The data on RIT in transformed NHL are derived from patients who were not candidates for high-dose chemotherapy and stem cell transplantation. The experience with ^{131}I -tositumomab has been summarized by Zelenetz and coauthors.²⁷ In this study, 71 patients with transformed lymphoma who had been enrolled in the five studies were identified. The median age was 59 years and the median number of prior therapies was four (range, 1–11). Twenty-eight percent of the patients had bone marrow involvement, 70% had bulky disease (> 5 cm), 57% had elevated LDH levels, and 52% had an International Prognostic Index score of 3 or more. The median follow-up was 19.4 months (range, 0.5–101). The ORR was 39%, with a CR rate of 25%. The median TTP for all patients was 4.3 months (range, 3.2–10.2) but for those who responded to the treatment, the median TTP was 20.2 months (range, 12.4–not reached). Five patients remain in remission beyond 40 months.

Aggressive Lymphomas

A significant proportion of patients with aggressive NHL can be cured with available chemotherapy or chemoimmunotherapy. Therefore, the available experience of RIT in aggressive NHL is limited to relapsed or refractory disease in patients who relapsed after or were not eligible for stem cell transplantation. Preliminary results have been reported evaluating ^{90}Y -ibritumomab tiuxetan in elderly patients with relapsed and primary refractory diffuse large B-cell lymphoma who were not candidates for stem cell transplantation.²⁸ A response was observed in 44% of 104 patients. The progression-free survival was reported separately for patients treated previously with regimens with or without rituximab and was 5.9 and 1.6 months, respectively. Although the treatment was generally well tolerated, 4 patients died due to adverse events.

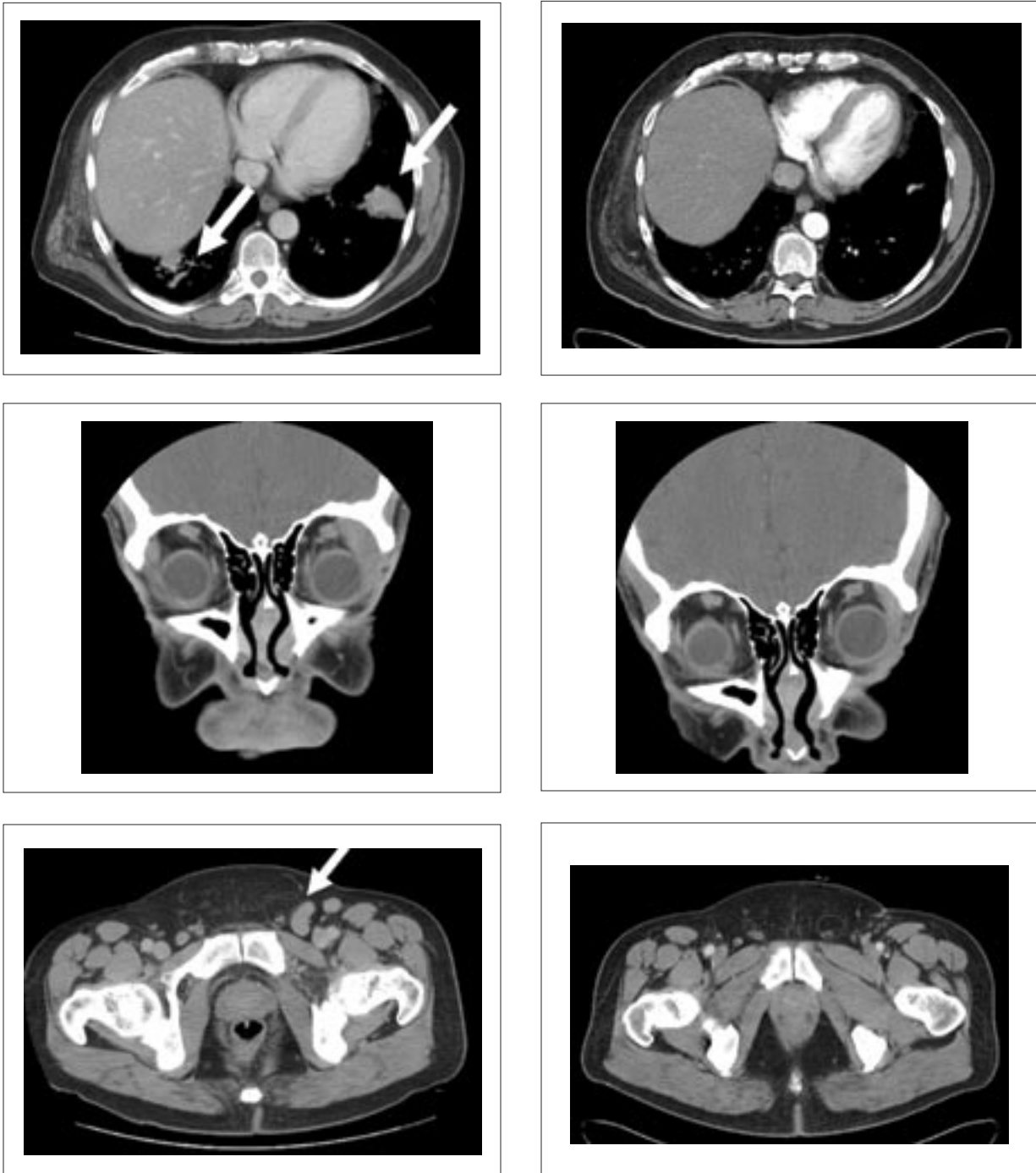
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Figure 1. Computerized tomography images before and 6 months after a single 32-mCi dose of ^{90}Y -ibritumomab tiuxetan for relapsed lymphoplasmacytoid non-Hodgkin lymphoma. The patient had left orbital proptosis from lacrimal gland involvement, bilateral lung metastases, splenomegaly, left inguinal adenopathy, and bone marrow involvement. This case demonstrates the ability of anti-CD20 radioimmunoconjugates to deliver effective radiotherapy to multiple sites of the body simultaneously without damage to the underlying normal tissues. The patient is now 3.5 years beyond treatment in an unmaintained complete remission, including a negative bone marrow.

Chemotherapy and Stem Cell Collection Following RIT

The myelosuppression seen after RIT raised the question of the feasibility of chemotherapy following RIT. Ansell and colleagues²⁹ examined the subsequent therapy administered to 58 patients who had relapsed after receiving 0.4 mCi/kg of ⁹⁰Y-ibritumomab tiuxetan. The percentage of patients administered each regimen was: 93% CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); 60% CVP (cyclophosphamide, vincristine, prednisone); 41% rituximab; 34% chlorambucil; 19% fludarabine; 14% ProMACE/CytaBOM (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, and methotrexate, with leucovorin rescue); and 22% (13/58) miscellaneous other regimens. Twenty-eight (48%) of the patients had transformed NHL (14 had the transformation before administration of ⁹⁰Y-ibritumomab tiuxetan and the rest had the transformation after its administration). Subsequent chemotherapy was feasible and tolerable. Twenty-eight percent of the patients received growth factors with their next chemotherapy and 2 patients required reduced doses due to persistent myelosuppression. Peripheral blood stem cell collection was also feasible, with 1 of 8 patients requiring bone marrow harvest after failing peripheral blood stem cell collection. All 8 patients engrafted. Although these data are encouraging, whenever possible if the patient is considered to be a candidate for autologous transplant stem cells should be collected before RIT. A single case report describes a successful autologous transplant following relapse after ¹³¹I-tositumomab.³⁰

Re-treatment with RIT

The data on re-treatment with RIT are limited, and clinical studies regarding the feasibility of this approach are ongoing. In the initial phase I study of ¹³¹I-tositumomab, 16 patients who had an initial response followed by a disease progression were re-treated with ¹³¹I-tositumomab. Nine of 16 patients responded and 5 had a CR.³¹ In the study by Kaminski and colleagues,³² patients who had a response to initial treatment with ¹³¹I-tositumomab could be re-treated. Thirty-two patients entered the study and 28 received the complete second treatment. Of these, 56% responded to therapy, with 25% achieving CR. Several patients who achieved a partial response initially had a CR with re-treatment. Wiseman and coauthors³³ reported preliminary results on a phase I trial in which all patients were treated with two sequential doses of ⁹⁰Y-ibritumomab tiuxetan. The first dose was 0.4 mCi/kg and the phase I dose levels for the second dose delivered 3–6 months after the first dose were 0.2, 0.3, or 0.4 mCi/kg. At the time

of the report, the maximum tolerated second dose was not established.

Summary

RIT with either ⁹⁰Y-ibritumomab tiuxetan or ¹³¹I-tositumomab is highly effective and safe for the treatment of low-grade NHL. RIT is highly effective in patients with refractory and relapsed disease, including patients with disease refractory to rituximab. RIT also induces high response rates in patients with newly diagnosed low-grade lymphomas. However, similar results in newly diagnosed patients can be achieved with other therapies and the role of RIT, including optimal sequencing with chemotherapy, will have to be established in randomized studies. Similarly, the value of re-treatment with RIT as well as RIT in aggressive NHL require further study.

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