Radioimmunotherapy is an effective but underutilized treatment option for patients with B-cell non-Hodgkin lymphoma in both the front-line and the relapsed/refractory setting.

Radioimmunotherapy for B-Cell Non-Hodgkin Lymphomas
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Background: Radioimmunotherapy (RIT) is a safe and effective therapeutic option for patients with indolent B-cell non-Hodgkin lymphomas (NHL), in both up-front and relapsed/refractory settings. Two approved agents (90Y-ibritumomab tiuxetan and 131I-tositumomab) are available in the United States. Both target CD20 with similar clinical outcomes but with unique clinical considerations and radiation precautions due to the use of varying radioisotopes.

Methods: This paper reviews the available evidence for these approved RIT agents and examines the recently published and ongoing clinical trials of potential novel indications for aggressive B-cell NHL.

Results: A pretreatment biodistribution evaluation required before administering the 90Y-ibritumomab tiuxetan therapeutic dose has been removed, which once limited its usage. The potential clinical applications of RIT include relapsed/refractory indolent B-cell NHL, diffuse large B-cell lymphoma, indolent lymphoma in the front-line setting, and mantle cell lymphoma. Multiple novel RIT agents are in preclinical and clinical development, and the addition of radiosensitizers or external-beam radiotherapy may act in synergy with RIT for both indolent and aggressive lymphomas. The risk of treatment-related myelodysplastic syndrome does not appear to be higher in patients treated with RIT over those receiving chemotherapy alone.

Conclusions: RIT is a safe, effective, and significantly underutilized therapy for patients with B-cell NHL, and many studies have demonstrated the efficacy of 90Y-ibritumomab tiuxetan and 131I-tositumomab for relapsed/refractory indolent B-cell lymphomas. Continued research to establish its efficacy for other lymphoma subtypes is warranted.

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The author has disclosed that this article discusses unlabeled/unapproved uses of 90Y-ibritumomab tiuxetan (Zevalin) for the treatment of diffuse large B-cell lymphoma and 131I-tositumomab (Bexxar) for the treatment of aggressive non-Hodgkin lymphoma.

Introduction
The treatment of B-cell non-Hodgkin lymphoma (NHL) has undergone significant transformation since the approval of rituximab in 1997 by the US Food and Drug Administration (FDA). This chimeric monoclonal antibody is specifically targeted to the CD20 molecule on the surface of mature B cells and B-cell lymphomas. While the endogenous role of CD20 is incompletely defined, evidence suggests a role in B-cell cycle progression as well as regulation of calcium influx necessary for B-cell activation. Rituximab exerts a cytotoxic effect via numerous different mechanisms including induction of apoptosis, antibody-dependent cell-mediated toxicity, and complement-mediated cytotoxicity. However, this
cytotoxic response requires the physical association of the monoclonal antibody with the particular target cell. Thus, a fractionated approach is necessary as evidenced by the approved regimens for rituximab as sole therapy and in combination with chemotherapy.

It was recognized early that the addition of a radionuclide to monoclonal antibodies would be a rational approach to achieving additional cytotoxic effects, particularly given the inherent radiosensitivity of most lymphomas. This approach, termed radioimmunotherapy (RIT), allows for the delivery of radionuclides directly to the surface of target tumor cells. Over time, as the radionuclide decays, the particles released cross several cell diameters, leading to a significant radiation exposure to cells not bound by the antibody. This “crossfire effect” is thought to lead to a significantly higher penetration within involved lymphoma lesions, particularly in the setting of bulky disease or in poorly perfused regions.1

To date, two RIT agents have been approved by the FDA for the treatment of B-cell NHL: yttrium-90 ($^{90}$Y)-ibritumomab tiuxetan (Zevalin) and iodine-131 ($^{131}$I)-tositumomab (Bexxar).2,3 Both agents are indicated for the treatment of relapsed or refractory CD20-positive lymphomas. In addition, $^{90}$Y-ibritumomab tiuxetan has an indication in the front-line setting following a complete response (CR) or a partial response (PR) to cytotoxic systemic therapy. $^{131}$I-tositumomab carries an additional indication for the treatment of transformed B-cell NHL. Both agents utilize radionuclides that decay by releasing beta particles (high-energy electrons) that exert lethal effects by causing double-strand DNA breaks in tumor cells.

**Characteristics of $^{90}$Y-Ibritumomab Tiuxetan and $^{131}$I-Tositumomab**

$^{90}$Y-ibritumomab tiuxetan

$^{90}$Y is not directly labeled to ibritumomab, so the linker-chelater tiuxetan is covalently bound to the antibody and holds the $^{90}$Y within a complex of carboxyl groups. As $^{90}$Y is a pure beta emitter, a second form of ibritumomab tiuxetan is provided using indium-111 (111In), which is primarily a gamma emitter used for dosimetric studies. On day 1, the patient begins with a pre-dosing regimen of 250 mg/m² of rituximab. Until recently, in the United States, the patient would then be infused with 5 mCi of 111In-ibritumomab tiuxetan to allow for a dosimetric analysis. Two to 3 days following the administration of the dosimetric dose, the patient returned for a nuclear medicine scan to determine biodistribution. The goal was to ensure that the uptake in radiosensitive organs such as the lungs, kidneys, and small bowel was less than that of the liver. Altered biodistribution has occurred in only a small proportion of patients by distribution on the scan. Assuming a normal distribution, the patient would return several days later for the therapeutic $^{90}$Y-ibritumomab tiuxetan treatment.

In November 2011, the FDA removed the requirement for the biodistribution scan, but the rituximab infusion on day 1 remains as part of the treatment. Removal of the biodistribution step has been supported by results presented at the 2011 American Society of Clinical Oncology annual meeting, where an analysis of five prospective trials revealed a true altered biodistribution in approximately 1% of patients on central review. Further, those patients were treated with $^{90}$Y-ibritumomab tiuxetan, and the clinical safety outcomes were similar to those in patients with a normal biodistribution.4

For the therapeutic dose, the patient again begins with a predosing regimen of rituximab followed by infusion of $^{90}$Y-ibritumomab tiuxetan. This infusion is performed as a slow push over approximately 10 minutes. Because of the pure beta emission from $^{90}$Y, once the ibritumomab tiuxetan infusion is complete, there are no significant radiation precautions for these patients.5 Less than 10% of unbound $^{90}$Y is excreted through the urinary system, and this is essentially complete within the first 12 to 24 hours. Dosing for $^{90}$Y-ibritumomab tiuxetan is based solely on the patient’s weight and platelet count. For patients with a platelet count greater than 150,000/μL, the prescribed dose is 0.4 mCi/kg up to a maximum of 32 mCi. For patients with a platelet count between 100,000 to 150,000/μL, the dose is 0.3 mCi/kg, again up to a maximum of 32 mCi.

$^{131}$I-Tositumomab

Tositumomab is labeled with $^{131}$I, a radionuclide with both beta and gamma emissions. Therefore, the same radionuclide can be used for both the dosimetric and therapeutic infusions. The dosage of $^{131}$I-tositumomab is based on the clearance of radiation from the body as measured on nuclear medicine scans. Patients begin on day 1 with a predosing infusion of unlabeled tositumomab. They then receive a 5-mCi dosimetric dose of the $^{131}$I-tositumomab. Immediately after that, a scan is performed to obtain whole-body gamma counts. Two additional scans are obtained 2 to 4 days later and again 6 to 7 days later. Based on the clearance of radiation from the body, the physician can calculate the therapeutic dose to be delivered. For patients with platelets of 150,000/μL or more, the goal is to deliver a dose that would lead to a total body exposure of 75 cGy. This target would be reduced to 65 cGy for patients with a platelet count between 100,000 and 150,000/μL.

One additional consideration for $^{131}$I-tositumomab is that any $^{131}$I that detaches from the antibody is typically taken up into the thyroid gland, and such accumulation could potentially lead to hypothyroidism as a late effect of treatment. To limit this exposure, patients are treated with potassium iodide orally beginning on day –1 and continuing for approximately 4 weeks. Any iodine excreted from the body occurs primarily through the urine.
131I-tositumomab is associated with a number of radiation precautions that must be carefully followed for patients treated with this agent.6 These include maintaining a distance of more than 2 meters from other people for extended periods of time, avoidance of sharing eating utensils, and washing clothes separately. The radiation physicist performs a radiation survey of the patient following the 131I-tositumomab infusion, and this measurement, along with the rate of clearance from the body as calculated by the nuclear medicine scans, allows for calculation of the amount of time patients must adhere to these radiation precautions.

RIT for Relapsed/Refractory Indolent B-Cell NHL

131I-Tositumomab

Several studies have been performed with 131I-tositumomab for patients with relapsed or refractory low-grade lymphoma. Overall response (OR) rates have ranged from approximately 50% to 80%, and CR rates have ranged from about 20% to 40%.

Kaminski et al7 reported a study of 59 patients with treatment-refractory NHL in which 28 were low-grade, 14 were transformed low-grade, and 17 were high-grade B-cell lymphomas. They reported an OR rate of 71%, with a significantly superior response rate of 83% for low-grade or transformed disease vs 44% for de novo aggressive lymphomas. CR rates overall were 34%, with half of the patients with low-grade or transformed lymphoma achieving a CR vs none of the patients with high-grade lymphoma. The authors reported a progression-free survival (PFS) of approximately 1 year, although PFS was greater than 20 months for those achieving a CR to therapy. Vose et al8 reported a similar study of patients with relapsed or refractory or transformed B-cell lymphomas. Forty-seven patients were treated, with an OR rate of 57% and a CR rate of 32%. In a separate study of treatment for chemotherapy-refractory indolent lymphoma, Kaminski et al9 reported on 60 patients, with OR and CR rates of 65% and 20%, respectively. An expanded access protocol of 273 patients with relapsed or refractory low-grade or transformed lymphomas revealed an OR rate of 58%, a CR rate of 27%, and a 3-year PFS rate of 68%.9

Many of the above studies were performed in patients who had not received prior rituximab. Horning et al10 reported on 40 patients with indolent or transformed lymphomas who had progressed on rituximab, showing an OR rate of 65%, a CR rate of 38%, and a median time to progression of 10.4 months.

90Y-Ibritumomab Tiuxetan

Wiseman et al11 reported on 30 patients with relapsed or refractory indolent or transformed lymphoma with platelet counts between 100,000 and 150,000/μL. Subjects received 0.3 mCi/kg of 90Y and achieved an OR rate of 83% and a CR rate of 37%, with a median time to progression of 9.4 months. Witzig et al12 reported on 54 patients with follicular lymphoma refractory to rituximab, giving 0.4 mCi/kg of 90Y with an OR rate of 74%, a CR rate of 50%, and a median time to progression of 6.8 months.

A randomized controlled trial of 90Y-ibritumomab tiuxetan vs rituximab was reported by Witzig et al in 2002. In this study of 143 patients, the OR rate was 80% with 90Y-ibritumomab tiuxetan vs 56% with rituximab. The respective CR rates were 30% and 16%. There was no significant difference in time to progression for all patients; however, for patients able to obtain a CR, the time to progression was 24.7 months for those receiving 90Y-ibritumomab tiuxetan vs 13.7 months for those receiving rituximab.13

The use of 90Y-ibritumomab tiuxetan earlier rather than later in relapsed or refractory disease appears to be important. Emmanouilides et al14 reported that patients with follicular lymphoma experienced a CR rate of 51% with 90Y-ibritumomab tiuxetan when treating patients in first relapse vs 28% for those treated later. Time to progression was also significantly better for those treated earlier (15.4 months vs 9.2 months).

In summary, RIT with either 131I-tositumomab or 90Y-ibritumomab tiuxetan has been shown to be an effective treatment option for patients with relapsed or refractory indolent B-cell NHL. OR rates range from approximately 60% to 80%, with nearly 40% of patients achieving a CR. These responses are also seen in patients who are rituximab refractory, and evidence suggests superior responses and PFS for patients treated in a first relapse rather than later in the course of the disease.

RIT for Indolent Lymphoma in the Front-line Setting

As recently as 5 years ago, the standard recommendation for patients with advanced-stage follicular lymphoma was chemoimmunotherapy followed by observation. As most physicians view follicular lymphoma as an indolent but ultimately incurable malignancy, and with most patients being treated above the age of 60 years, the assumption was that it would be best to achieve a good response to standard agents and then to follow for the eventual relapse.

Recently, Bachy et al15 published an analysis of overall survival (OS) in patients treated for follicular lymphoma. Survival curves for patients obtaining a CR vs a PR to front-line therapy diverged early and maintained a significant difference over long follow-up, supporting the concept that methods of consolidating the response to chemotherapy may affect OS. This would be particularly important for patients obtaining a PR to front-line therapy.

In 2008, Morschhauser et al16 reported their results of a randomized controlled trial (the FIT trial) compar-
ing ⁹⁰Y-ibritumomab tiuxetan vs no further therapy in patients who obtained a CR or a PR to standard front-line chemotherapy regimens. Investigators were allowed to utilize their front-line regimen of choice. Subjects were restaged upon completion of chemotherapy, and those achieving a CR or a PR were then randomized between the control and the ⁹⁰Y-ibritumomab tiuxetan arms. Patients randomized to ⁹⁰Y-ibritumomab tiuxetan received the standard dosage of 0.4 mCi/kg up to a maximum of 32 mCi. Following induction therapy, the CR rate was 53% in the observation arm and 52% in the ⁹⁰Y-ibritumomab tiuxetan arm. Following randomization, the final CR rates were 53% and 87%, respectively. This represented a conversion from PR to CR with the addition of ⁹⁰Y-ibritumomab tiuxetan in approximately three-quarters of the patients receiving RIT. The median PFS for patients in the control arm and the RIT arm was 15 vs 49 months for all responders, 6 vs 30 months for partial responders, and 32 vs 92+ months for complete responders, respectively. Patients randomized to receive ⁹⁰Y-ibritumomab tiuxetan exhibited a greater than 5-year improvement in the time to next treatment compared with controls. No differences in OS were noted in follow-up to this point, given the indolent nature of follicular lymphoma.

One criticism of the FIT trial has been that only approximately 14% of subjects received rituximab during the induction phase. However, at the time the trial was conceived and written, rituximab was not yet a standard agent in the front-line setting in countries participating in the trial. Due to the small number of rituximab-treated patients, there was insufficient power to detect a difference in final CR rates (93% for the ⁹⁰Y-ibritumomab tiuxetan arm vs 71% for the observation arm) or in rates of conversion from PR to CR (71% vs 42%, respectively). The Southwest Oncology Group (SWOG) recently presented results of S0016, a randomized controlled trial for patients with advanced-stage follicular lymphoma comparing 6 cycles of standard R-CHOP chemotherapy (consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab) with 6 cycles of CHOP followed by a single infusion of ¹³¹I-tositumomab. A total of 526 patients were eligible for analysis, and after 5 years of follow-up, no significant differences in OR rates, CR rates, or 2-year PFS or OS were observed. In addition, there were also no differences between the arms for toxicity (hematologic or nonhematologic) or for secondary malignancies, including secondary myelodysplastic syndrome (MDS). In the end, a single infusion of ¹³¹I-tositumomab appears to be equivalent to 6 infusions of rituximab. The follow-up trial (S0801) examining R-CHOP followed by ¹³¹I-tositumomab consolidation followed by maintenance rituximab has recently completed accrual.

Five additional studies of ⁹⁰Y-ibritumomab tiuxetan consolidation with rituximab-based induction regimens have been reported, most utilizing abbreviated chemotherapy regimens. Hainsworth et al reported on a phase II trial of 4 infusions of rituximab followed by 3 cycles of rituximab-based chemotherapy prior to ⁹⁰Y-ibritumomab tiuxetan consolidation. CR rates improved from 30% following induction therapy to 72% following RIT consolidation. At 67 months of follow-up, the estimated PFS and OS rates were 64% and 96%, respectively. Jacobs et al reported the results of a phase II trial of 3 cycles of induction chemotherapy followed by consolidation with ⁹⁰Y-ibritumomab tiuxetan and 4 infusions of rituximab. CR rates improved from 46% after induction therapy to 89% on restaging PET/CT following RIT consolidation. Three studies using 4 or more cycles of rituximab and a fludarabine-based cytotoxic backbone followed by RIT consolidation, with or without adjuvant rituximab maintenance, have been reported, with PR to CR conversion rates of 60% to 100% following RIT. Together, these data suggest that RIT consolidation following induction therapy improves CR rates, even for patients previously treated with rituximab.

Rose et al recently presented a meta-analysis of RIT consolidation in the front-line setting for patients with advanced-stage follicular lymphoma. Reviewing seven reported studies with at least 2-year follow-up data, their analysis showed 2-year and 5-year PFS rates as 77% and 56%, respectively. Kaminski et al reported on the use of ¹³¹I-tositumomab as sole single-agent therapy for 76 previously untreated patients with advanced-stage follicular lymphoma. They found an OR rate of 95% and a CR rate of 75% with this single infusion. The authors recently updated the study with a median 10-year follow-up. Median response duration was 6 years, with 40% of patients remaining in remission at 10 years. There was a significant difference between patients achieving a CR vs a PR to ¹³¹I-tositumomab, with a median PFS of 11 years and an 82% OS rate for patients obtaining a CR. At 10 years, only a single case of MDS has been observed at 8 years following ¹³¹I-tositumomab. Pica et al recently published the results of a 50-patient study of single-agent ⁹⁰Y-ibritumomab tiuxetan for newly diagnosed advanced-stage follicular lymphoma. They reported a CR rate of 82% and an OR rate of 93%, with favorable myelosuppression and only 4% of patients requiring transfusion support. The 2-year event-free survival rate was 85%.

Several other prospective studies of RIT in the front-line setting for advanced-stage follicular lymphoma have been reported. Zinzani treated 26 patients with 6 cycles of fludarabine and mitoxantrone followed by ⁹⁰Y-ibritumomab tiuxetan. They reported an OR rate of 81%, a CR rate of 50%, and a 3-year PFS rate of 90%. Press et al studied 90 patients treated with ¹³¹I-tositumomab as consolidation after front-line chemo-
therapy and reported OR and CR rates of 90% and 67%, respectively. Leonard et al\textsuperscript{28} reported a similar study of 35 patients using \textsuperscript{131}I-tositumomab following 4 cycles of fludarabine, observing an OR rate of 100% and an 86% CR rate, with a 5-year OS rate of 86%. Fowler et al\textsuperscript{30} recently presented their data on 49 patients treated with 4 cycles of rituximab, fludarabine, mitoxantrone, and dexamethasone followed by consolidation with \textsuperscript{90}Y-ibritumomab tiuxetan and rituximab maintenance. They reported projected 5-year OS and PFS rates of 93% and 74%, respectively.

RIT plays an important role in the front-line setting, whether used as a single agent or as planned consolidation following standard chemoimmunotherapy. The use of RIT is superior to observation following front-line treatment, resulting in improved PFS, superior time to next treatment, and conversion of PRs to CRs. Follow-up is too brief to date to show a significant improvement in OS. For patients who refuse chemotherapy or who are not suitable candidates, RIT as a single agent should be considered as a relatively nontoxic alternative, with OR rates of 90% to 100%, CRs rates of 70% to 80%, and lengthy PFS, particularly for patients obtaining a CR.

**RIT for Diffuse Large B-Cell Lymphoma**

Morschhauser et al\textsuperscript{31} reported on 104 patients with relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL) treated with \textsuperscript{90}Y-ibritumomab tiuxetan. Three groups were enrolled: patients who failed primary induction, those who were in relapse and rituximab-naive, and those who relapsed following rituximab-based therapy. The OR rates were 52%, 53%, and 19%, respectively. CR rates ranged from 12% to 40%, with the median PFS in the three groups ranging from 1.6 to 5.9 months.

Several phase II studies have examined the role for RIT consolidation in DLBCL patients following CHOP-based chemotherapy. Zinzani et al\textsuperscript{32} reported on 20 patients who received 6 cycles of CHOP chemotherapy alone, followed by a single infusion of RIT. The OR rate was 100%, with a 75% CR rate after CHOP and a 95% CR rate following \textsuperscript{90}Y-ibritumomab tiuxetan, representing an 80% conversion rate of PR to CR with consolidation. The 2-year PFS rate was 75% in this high-risk population.

Hamlin et al\textsuperscript{33} reported results of a similar trial of 61 elderly patients with DLBCL, all with high-risk features. They received R-CHOP for 6 cycles, followed by planned consolidation with \textsuperscript{90}Y-ibritumomab tiuxetan. CR rates were 75% following R-CHOP and 90% following RIT as measured by best response. Of the 50 patients assessed for RIT after chemotherapy, 44 (88%) received the planned RIT consolidation, with 86% of those receiving the full 0.4 mCi/kg dose of \textsuperscript{90}Y-ibritumomab tiuxetan. Hematologic toxicity following RIT consolidation was similar to that seen with on-label use of \textsuperscript{90}Y-ibritumomab tiuxetan. The estimated OS and PFS rates at 5 years for patients receiving RIT consolidation were 84% and 75%, respectively.

These data are congruent with a similar trial by Zinzani et al\textsuperscript{34} of elderly DLBCL patients receiving 4 cycles of R-CHOP followed by planned consolidation with \textsuperscript{90}Y-ibritumomab tiuxetan, reporting 2-year OS and PFS rates as 86% and 85%, respectively. SWOG 0433 examined the role of \textsuperscript{131}I-tositumomab in elderly DLBCL patients following induction therapy with 6 cycles of R-CHOP and 2 additional cycles of CHOP alone.\textsuperscript{35} The estimated 1-year OS and PFS rates were 85% and 75%, respectively.

Based on these data, an international phase III randomized controlled trial recently opened to determine the value of RIT consolidation following standard rituximab-based chemotherapy for elderly DLBCL patients with one or more age-adjusted risk factors. All patients will receive 6 cycles of chemotherapy; if they achieve a CR, they will be randomized to consolidation or no further therapy. The primary endpoint will be OS, with an estimate that \textsuperscript{90}Y-ibritumomab tiuxetan will reduce the 2-year risk of mortality by 50%.

SWOG S1001 is a prospective trial to examine the potential role of RIT in the treatment of patients with stage I or II DLBCL. All patients will receive 3 cycles of R-CHOP chemotherapy and will then be restaged by PET/CT. Patients with a CR will receive 1 additional cycle of R-CHOP, for a total of 4 cycles. Those with a PR will receive standard-dose involved-field radiotherapy followed by a single infusion of \textsuperscript{90}Y-ibritumomab tiuxetan.

**RIT for Mantle Cell Lymphoma**

Wang et al\textsuperscript{36} conducted a study of 34 patients treated with single-agent \textsuperscript{90}Y-ibritumomab tiuxetan for relapsed or refractory mantle cell lymphoma (MCL) and reported an OR rate of 31%, a CR rate of 15%, and a median event-free survival of 28 months for responders.

Two studies have reported on the use of RIT in newly diagnosed MCL. Zelenetz et al\textsuperscript{37} treated 25 MCL patients with front-line \textsuperscript{131}I-tositumomab, and 21 proceeded to CHOP consolidation. The OR rate was 86%, the CR rate was 67%, and the OS rate at 2 years was 92%. Smith et al\textsuperscript{38} treated 53 patients with newly diagnosed MCL with 4 cycles of R-CHOP chemotherapy followed by planned \textsuperscript{90}Y-ibritumomab tiuxetan consolidation. The OR rate was 88% after RIT, with a CR rate of only 13% after R-CHOP but 55% after \textsuperscript{90}Y-ibritumomab tiuxetan. The 2-year OS rate was 90%, with a median PFS of 31 months.

Beaven et al\textsuperscript{39} recently reported the results of a phase I study combining \textsuperscript{90}Y-ibritumomab tiuxetan with bortezomib in patients with relapsed or refractory MCL or indolent B-cell lymphoma. Using standard doses of \textsuperscript{90}Y-ibritumomab tiuxetan and 1.5 mg/m\textsuperscript{2} bortezomib, they did not obtain dose-limiting toxicity. Objective responses for these relapsed patients were promising, with an OR rate of 50% and a CR rate of 42%. Based on
these data, these investigators have recently opened a phase II trial of this novel combination in patients with relapsed or refractory MCL.

**Repeat-Dose RIT**

While the principal dose-limiting side effect of the approved agents is transient yet significant myelosuppression, patients recover blood counts effectively following RIT and in a predictable fashion. The delayed but nearly inevitable relapses of follicular lymphoma after RIT and the lower response rates of more aggressive lymphomas have led investigators to consider the potential value of repeat-dose RIT. Illidge et al\(^40\) reported on 16 patients with relapsed or transformed follicular lymphoma treated with weekly rituximab followed by 2 infusions of \(^{131}\)I rituximab. The cumulative total body exposure was 120 cGy. The OR rate was 94%, the CR rate was 50%, and the median time to progression was 20 months.

Shah et al\(^41\) reported on a retrospective analysis of patients who had received multiple infusions of \(^{90}\)Y-ibritumomab tiuxetan. Eighteen patients received 2 doses at a median of 16.6 months apart. Grade 3/4 neutropenia, thrombocytopenia, and OR rate were 35%, 41%, and 89% for the first RIT course, respectively, and 28%, 44%, and 77% for the second course. Similar safety and efficacy have been reported with \(^{131}\)I-tositumomab re-treatment.\(^42\)

More recently, Illidge et al\(^43\) reported early results of a phase II trial of planned tandem \(^{90}\)Y-ibritumomab tiuxetan infusions as sole therapy for patients with advanced follicular lymphoma. A total of 72 patients received \(^{90}\)Y-ibritumomab tiuxetan, and only 17% had the second infusion held due to failure of myelosuppression to resolve by 12 weeks. For all patients, the OR rate at the end of treatment was 96% (57% CR) compared with 97% and 64%, respectively, for those who received both planned infusions. Despite the repeat dosing schedule, myelosuppression was manageable, with only 8 patients requiring transfusion support.

One important consideration for a repeat dosing approach with \(^{90}\)Y-ibritumomab tiuxetan or \(^{131}\)I-tositumomab is that both antibodies are of murine origin, and patients previously exposed may form human antimurine antibodies (HAMA). Any patient being considered for repeat administration of either agent should be tested for the presence of HAMA prior to re-treatment since unrecognized presence of such antibodies could potentially trigger an anaphylactic reaction.\(^44\) In the \(^{90}\)Y-ibritumomab tiuxetan tandem infusion study by Illidge et al\(^43\) discussed above, the development of HAMA was 5.6%.

**Novel RIT Agents for B-Cell NHL**

CD20 is not the only cell surface marker relatively specific for B cells and B-cell malignancies. CD22 is another rational target for RIT, and epratuzumab is a humanized monoclonal antibody directed to CD22. This agent, labeled with \(^{90}\)Y, is currently being investigated in a number of clinical trials. Morschhauser et al\(^45\) reported the results of a phase I/II study of a fractionated approach with \(^{90}\)Y-epratuzumab in NHL, with an OR rate of 78% and a CR rate of 56%.

\(^{90}\)Y-epratuzumab is currently being used in a phase I/II trial for patients with aggressive or transformed B-cell NHL. Patients are treated with unlabeled veltuzumab (anti-CD20) in 4 weekly infusions, with 2 infusions of the labeled epratuzumab given the third and fourth weeks. An early interim analysis has recently been completed, with promising results to be presented soon. This combination is also currently being investigated in a phase II study as sole treatment for newly diagnosed follicular lymphoma.

CD19, CD45, CD74, and several other targets have been sources for development of other radiolabeled monoclonal antibodies for B-cell and T-cell lymphomas.\(^46-49\) Other novel approaches include the use of hapten or bispecific antibodies for pretargeting.\(^50,51\)

**Combining RIT and External-Beam Radiotherapy**

Indolent B-cell NHLs are both exquisitely radiosensitive and typically multifocal in presentation. Several studies have shown that even very low doses of involved field radiotherapy (IFRT) for bulky or symptomatic follicular lymphoma result in high rates of palliation, with overall and CR rates ranging from 82% to 95% and 55% to 84%, respectively.\(^52-54\)

Some patients treated with RIT have several measurable sites of disease but only one or a couple of large foci. Given the lower response rates in sites of bulky disease with RIT alone as well as the high response rates with low-dose IFRT, a rational approach may be to incorporate both RIT and IFRT to larger lesions for the same patient. Burdick et al\(^55\) reported on a series of 11 patients with relapsed or refractory bulky follicular lymphoma treated with 2,400 cGy IFRT prior to RIT with \(^{90}\)Y-ibritumomab tiuxetan. Nearly 20% of patients required an extended break between the external-beam radiotherapy (EBRT) and RIT. The CR rate at 4 months was 64%, with no relapses within the radiotherapy fields. Median PFS was reported as 17.5 months. However, given the radiosensitivity of indolent lymphomas and the potential toxicity and inconvenience of several weeks of daily IFRT, a more rational approach may be the combination of low-dose IFRT and RIT. Tomblyn\(^56\) reported results of 13 patients treated with 400 cGy in 2 fractions to bulky disease between the dosimetric and therapeutic infusions of RIT. With a median follow-up of 14 months, 11 patients (85%) had obtained a CR to therapy. None relapsed in the radiotherapy fields. The PFS rate for patients obtaining a CR was 100%. Two patients with only a PR went on to receive allogeneic he-
matopoietic stem cell transplant and died of transplant-related toxicities.

The combination of RIT with involved-field radiotherapy to sites of bulky disease appears to be safe and effective for patients with B-cell lymphomas. The underlying mechanism of this therapeutic synergy is poorly understood, but oxidative stress caused by radiotherapy may induce an upregulation in CD20 expression. This boost of antigenic presentation may allow greater targeting of RIT to the surface of these lymphoma cells.

**RIT and Risk of MDS**

Perhaps the most frequently cited concern of referring physicians is that RIT has the potential to lead to secondary malignancies, particularly MDS. The annualized risk of MDS from the front-line RIT consolidation trial was reported as 0.55% per year. With a median 10-year follow-up, Kaminski et al reported a single case of MDS out of 76 previously untreated patients who received a single treatment with 131I-tositumomab. Czuczman et al reviewed the records of 746 patients treated with 90Y-ibritumomab tiuxetan, with a median follow-up of approximately 4.5 years, and found a total of 19 (2.5%) who developed MDS at a median of nearly 2 years following RIT and 5.6 years following a diagnosis of lymphoma. This corresponded to an annualized MDS rate of 0.7% per year following RIT. Of note, the vast majority of these MDS cases expressed abnormalities of chromosomes 5 and/or 7, commonly seen in patients heavily pretreated with alkylating agents. The expected annualized rate of treatment-related MDS for patients receiving alkylator-based systemic therapy alone or in combination with rituximab is approximately 1% per year.

With significant follow-up, the use of RIT does not appear to significantly increase the risk of secondary MDS above the risk of chemotherapy alone.

**Conclusions**

Radioimmunotherapy is a safe, effective, and significantly underutilized therapy for patients with B-cell non-Hodgkin lymphomas. Multiple studies have demonstrated the efficacy of 90Y-ibritumomab tiuxetan and 131I-tositumomab in the setting of relapsed/refractory indolent B-cell lymphomas. However, to date no comparative study has shown an advantage in overall survival, as expected when dealing with indolent diseases. More recently, 90Y-ibritumomab tiuxetan has been approved for the front-line treatment of follicular lymphoma for patients responding to induction chemotherapy and carries a National Comprehensive Cancer Network Category 1 indication for this use. Several prospective studies have reported improvements in safety and efficacy for approved radioimmunotherapy agents in patients with aggressive B-cell lymphomas as well. A randomized controlled trial of 90Y-ibritumomab tiuxetan consolidation for elderly patients with diffuse large B-cell leukemia will open soon and will help to clarify these issues. Evidence exists for a role for radioimmunotherapy in mantle cell lymphoma as well, and trials will soon offer guidance regarding the role of concurrent radiosensitizing drugs in this setting. Multiple other targets for radioimmunotherapy agents are specific for non-Hodgkin lymphomas, and a number of novel radiolabeled monoclonal antibodies are currently being developed in the preclinical and clinic settings. Despite the concerns over second malignancies induced by radioimmunotherapy, the risk of myelodysplastic syndrome does not appear to be elevated over the risk associated with the use of chemotherapy alone.

**References**

17. Press OW, Unger JM, Bazzi RM, et al. A phase 2 trial of CHOP chemotherapy followed by tositumomab/iodine I 131 tositumomab for pre-