Harnessing the Energy: Development of Radioimmunotherapy for Patients with Non-Hodgkin’s Lymphoma

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This article discusses Yttrium-90-ibritumomab tiuxetan (Bayer Schering Pharma AG, Spectrum Pharmaceuticals, Inc.), a radioimmuno-therapeutic agent, to minimize the systemic effects of radiation, as therapy in NHL patients with relapsed low-grade NHL and for consolidation therapy after frontline chemotherapy.

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ABSTRACT
Radioimmunotherapy (RIT) combines the use of targeted monoclonal antibodies with radionuclides for the treatment of non-Hodgkin’s lymphoma (NHL), taking advantage of its inherent radiosensitivity. A number of trials have shown significantly higher response rates and longer progression-free survival times in patients treated with the CD20-targeted radioimmunoconjugate yttrium-90-ibritumomab tiuxetan compared with the standard of care. Furthermore, these benefits have also been shown in heavily pretreated patients who relapsed or were resistant to rituximab. Currently, a number of different treatment regimens and strategies are available for the treatment of NHL patients. Therefore, in an attempt to minimize toxicity, maximize efficacy, and improve survival, it is crucial to appropriately select patients who are good candidates for individual treatment approaches. A strategy for patient selection has been developed, including the use of existing patient assessment tools, such as the Follicular Lymphoma International Prognostic Index, to determine the optimal regimen for patients with follicular lymphoma according to their disease characteristics and physical condition. Patients who are fit make ideal candidates for potentially curative regimens, which include induction chemotherapy with or without immunotherapy followed by RIT consolidation and, potentially, maintenance therapy. Patients who are considered “compromised” would also benefit from induction treatment and RIT consolidation, with a view to reducing the lymphoma burden and decreasing the risk for disease progression. “Frail” patients would be better suited to supportive therapy to control symptoms. This paper explores factors that should be considered when assessing
whether a patient is a good candidate for treatment with RIT, and aids physicians in the selection of the most appropriate therapy for each patient group. The Oncologist 2009;14(suppl 2):4–16

**Basic Principles of Radioimmunotherapy**

**Monoclonal Antibodies: A Targeted Approach**

The B-cell antigen CD20 provides an excellent immunotherapeutic target for non-Hodgkin’s lymphoma (NHL) because of its expression patterns [1, 2]. Over 90% of B-cell tumors express CD20, and it is present exclusively on mature B cells and is further amplified in malignant B cells [3]. CD20 is absent from hematopoietic stem cells, pro-B-cells, and normal plasma cells, and does not accumulate as a free protein [3]. Furthermore, when bound by anti-CD20 antibody, CD20 does not shed from the cell surface [4].

The use of targeted monoclonal antibodies in the treatment of cancer has become more prevalent over the last decade. The most widely used antibody, rituximab, is a CD20-targeted monoclonal antibody used as a single agent and in combination therapy in both follicular and relapsed indolent NHL. Monotherapy is often used in patients with a low tumor burden [5, 6]. Rituximab is also often combined with chemotherapy to treat several hematologic malignancies, including low-grade lymphomas, follicular lymphoma (FL), and more aggressive lymphomas [7–9]. Rituximab is indicated for the treatment of patients with: relapsed or refractory low-grade or follicular NHL; nonprogressing low-grade NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy; previously untreated follicular B-cell NHL in combination with CVP; and previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens [10]. Rituximab-CHOP (R-CHOP) and rituximab-CVP have been demonstrated to produce superior outcomes in several trials, yielding overall response rates (ORRs) of 80%–95% and longer survival times in low-grade FL and aggressive NHL [7–9]. The superior survival outcomes have been attributed to higher complete response (CR) rates, which are higher in patients with aggressive NHL who receive the R-CHOP combination relative to treatment with chemotherapy alone (76% versus 63%; \( p = .005 \)), as is the 2-year overall survival (OS) rate (70% versus 57%; \( p < .001 \)) [9]. Monoclonal antibodies are also used effectively to treat solid tumors.

**Radioimmunotherapy for NHL**

Monoclonal antibodies can be conjugated with radionuclides, becoming radioimmunotherapy (RIT), which harnesses the targeted activity of the antibody to directly deliver radiation to destroy neoplastic cells at the tumor site, unlike the more diffuse delivery historically employed with conventional radiotherapy. This combination of the biologic and radiolytic mechanisms of action is ideal for the treatment of poorly vascularized or bulky tumors, because malignant cells not directly accessible to the monoclonal antibody are still affected by the ionizing radiation of the radionuclide [11]. This “crossfire” effect of targeting radiation to tumor cells expressing a particular antigen is particularly useful, because with RIT a lower overall dose of radiation is necessary, thus limiting whole-body exposure to radiation and minimizing toxicity to normal cells and organs [12].

A number of factors contribute to the effectiveness of RIT, including the target antigen, specific radionuclide emission properties, and the chemical stability of radioimmunoconjugates [11]. Furthermore, as lymphomas are inherently radiosensitive, CD20-targeted RIT is a promising treatment option for this tumor type [13–15].

**Current RIT Treatment Options**

A crucial consideration that dramatically affects the outcome of treatment with RIT is the choice of radionuclide to be conjugated with the chosen monoclonal antibody. The radioimmunoconjugate iodine-131 (\(^{131}\text{I}\))-tositumomab (Bexxar®; GlaxoSmithKline, Research Triangle Park, NC) consists of the murine IgG2a \( \lambda \) monoclonal antibody directed against the CD20 antigen covalently linked to \(^{131}\text{I}\). Although radioiodinated (\(^{131}\text{I}\)) antibodies are used for the treatment of B-cell lymphomas, their long half-life and the possibility of separation from the antibody can lead to rapid excretion or accumulation in the thyroid, or both [16–18]. The nature of the \( \gamma \) emissions of \(^{131}\text{I}\) means the same agent can be used for both imaging and therapeutic purposes. Therefore, shielding, careful disposal of bodily fluids, and, in some cases, hospitalization are necessary precautions with any treatment containing \(^{131}\text{I}\).

An alternative radionuclide is the radiometal yttrium-90 (\(^{90}\text{Y}\)), which emits \( \beta \) radiation. It has been reported that radioimmunoconjugates containing \(^{90}\text{Y}\) deliver radioactivity to tumors more effectively than \(^{131}\text{I}\) and are associated with a better therapeutic index [19, 20]. Another advantage of \(^{90}\text{Y}\) is the minimal risk for exposure, because of its emission of pure \( \beta \) radiation.

As metals cannot be directly incorporated into antibod-
ies, chelator linkers have been developed, such as MX-DTPA (tiuxetan), which forms a stable chelate of radionuclide and antibody without compromising antibody specificity, altering the metabolism of the complex, or allowing measurable elution of $^{90}$Y [21, 22]. Tiuxetan strongly chelates $^{90}$Y and covalently binds to the IgG$_1$ anti-CD20 monoclonal antibody ibritumomab, forming the therapeutic radioimmunoconjugate $^{90}$Y-ibritumomab tiuxetan (Zevalin®; Spectrum Pharmaceuticals, Inc., Irvine, CA; Bayer Schering Pharma AG, Berlin, Germany) (Fig. 1) [4]. For imaging purposes, indium-111 ($^{111}$In), a γ emitter, is used as a substitute for $^{90}$Y [23, 24]. Ibritumomab is the parent murine antibody from which the chimeric murine and human monoclonal antibody rituximab is derived [11]. Both ibritumomab and rituximab target the CD20 antigen found on B cells [25] and have been shown to have antiproliferative and proapoptotic effects in vitro [26].

Patients treated with β radiation emitted by $^{90}$Y-ibritumomab tiuxetan (half-life, 64 hours) do not need to be isolated [27] and can be treated in an outpatient setting [28]. Key differences between $^{90}$Y-ibritumomab tiuxetan and $^{131}$I-tositumomab are highlighted in Table 1.

**INDICATIONS FOR RIT**

**Relapsed or Refractory Low-Grade or Follicular B-Cell NHL**

The initial U.S. indication for $^{90}$Y-ibritumomab tiuxetan, the first RIT approved by the U.S. Food and Drug Administration (FDA), is for the treatment of patients with relapsed or refractory low-grade or follicular B-cell NHL, and for those with FL refractory to rituximab. This indication is supported by a number of clinical trials that have been performed in patients with NHL.

A phase I/II trial compared two dose levels of rituximab (100 mg/m$^2$ and 250 mg/m$^2$) followed by $^{90}$Y-ibritumomab tiuxetan (three dose levels: 0.2 mCi/kg, 0.3 mCi/kg, and 0.4 mCi/kg) in patients with relapsed or refractory CD20$^+$ B-cell, low- or intermediate-grade NHL or mantle cell lymphoma to determine the maximum-tolerated dose (MTD) and evaluate safety and efficacy [29]. All patients had received prior chemotherapy, with a median of two prior regimens (range, 1–7), and 47 (92%) had received prior anthracyclines. The MTD of $^{90}$Y-ibritumomab tiuxetan was found to be 0.4 mCi/kg, or 0.3 mCi/kg for patients with baseline platelet counts of 100,000 –149,000/μl.

A larger phase III trial was performed in a similar patient group to assess the ORR using an independent, blinded, lymphoma expert panel [30]. Patients were treated with either four doses of rituximab (375 mg/m$^2$) weekly ($n = 70$) or a single dose of $^{90}$Y-ibritumomab tiuxetan (0.4 mCi/kg) preceded by two doses of rituximab (250 mg/m$^2$) and one dose of $^{111}$In-ibritumomab tiuxetan for imaging and dosimetry ($n = 73$). An ORR of 80% was observed for those treated with RIT, compared with 56% for those who received rituximab alone ($p = .002$), with CR rates of 30% and 16%, respectively ($p = .04$). The median duration of response was 14.2 months in the RIT group, versus 12.1 months in the rituximab group ($p = .6$), although the rates of durable responses ≥6 months were 64% and 47%, respectively ($p = .030$). The most frequent adverse event (AE) associated with RIT was reversible myelosuppression, with median durations of 27 days (absolute neutrophil count), 23 days (platelets), and 15 days (hemoglobin). A

![Figure 1. Yttrium-90 ($^{90}$Y)-ibritumomab tiuxetan binding to a B cell via the CD20 antigen.](http://theoncologist.alphamedpress.org/Downloaded from)
Table 1. Key differences between 90-Y ibritumomab tiuxetan and 131-I tositumomab

<table>
<thead>
<tr>
<th>Properties</th>
<th>90-Y ibritumomab tiuxetan</th>
<th>131-I tositumomab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific targeting</td>
<td>Malignant and non-malignant CD20-positive B cells</td>
<td>Malignant and non-malignant CD20-positive B-cells</td>
</tr>
<tr>
<td>Radiation</td>
<td>Pure beta emitter</td>
<td>Gamma and beta emitter</td>
</tr>
<tr>
<td>Physical properties</td>
<td>Rapid radioactive decay to 90-Zr, a stable and non-toxic daughter product</td>
<td>Decays to produce both beta and gamma emissions</td>
</tr>
<tr>
<td>Half-life</td>
<td>64 hours</td>
<td>8 days</td>
</tr>
<tr>
<td>Energy</td>
<td>2.3 MeV</td>
<td>Principal beta emission: 2.9 MeV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Principal gamma emission: 364.5 keV</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td>Single dose, combined with rituximab pre-infusions; typically completed within 1 week</td>
<td>Single dose, combined with tositumomab pre-infusion, completed within 7–14 days Gamma scans are helpful for dosimetry</td>
</tr>
<tr>
<td>Dosing</td>
<td>Optimal dose is based on patient’s baseline platelet count and body weight</td>
<td>Dose to deliver 65–75 cGy total-body dose, based on clearance of tositumomab from patient (specific dosimetry)</td>
</tr>
<tr>
<td>Stability</td>
<td>Stable at 4°C for 48 hours</td>
<td>Stable at 2–8°C for &lt;8 hours</td>
</tr>
<tr>
<td>In vitro</td>
<td></td>
<td></td>
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<tr>
<td>Overall response rate</td>
<td>80%</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>12.6 months&lt;sup&gt;a&lt;/sup&gt; 14.2 months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10.4 months (24.5 months for responders, not reached for complete responders) 8.4 months (for responders, median duration of response &gt;47 months for complete responders)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Moderate hematologic toxicity that usually recovers by 13 weeks</td>
<td>Moderate hematologic toxicity that usually recovers by 13 weeks</td>
</tr>
<tr>
<td>Safety</td>
<td>No isolation needed, hospital-based outpatient therapy is feasible Bodily fluids may be radioactive</td>
<td>Lead shielding for handling is required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most US states allow for outpatient treatment. Radiation safety (keep away from children and pregnant women; separate eating utensils and sleeping in a separate bed) should be followed for 1 week after therapeutic dose</td>
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<sup>a</sup>Gregory, Hohloch, Gisselbrecht www.TheOncologist.com
study of long-term responders from four clinical trials of patients with relapsed or refractory NHL who were treated with $^{90}$Y-ibritumomab tiuxetan demonstrated that ~60% of CR patients achieved long-term remissions lasting >24 months, suggesting that the achievement of a CR may be used as a surrogate marker for achieving long-lasting remissions [31].

Using the reduced dose of 0.3 mCi/kg, $^{90}$Y-ibritumomab tiuxetan was investigated in 30 mildly thrombocytopenic (100,000–149,000 platelets/µL) patients with relapsed or refractory low-grade NHL [32]. Although estimated radiation rates were well below the study-defined maximums (<2,000 cGy for uninvolved major organs and <300 cGy for red marrow), the ORR was 83% (CR rate, 37%) in the intent-to-treat population, and a median time to progression of 12.6 months was observed in the 25 responders [32]. Although a dose-reduction rule was included in the study profile, no patients required a reduction because no toxicity crossed the threshold of the protocol-defined limit.

The safety data from the main $^{90}$Y-ibritumomab tiuxetan clinical trials, which included 349 patients, were analyzed for FDA approval [11, 33]. Infusion reactions, an AE associated with rituximab, were typically grade 1 or 2. AEs were primarily hematologic in nature, with grade 2 neutropenia, thrombocytopenia, and anemia observed in 30%, 10%, and 3% of patients, respectively, following use of the 0.4 mCi/kg dose, with nadirs occurring at 7–9 weeks [11, 33]. However, only 7% of patients were hospitalized because of infection (3% with neutropenia), possibly reflecting the low incidence (<1%) of mucositis associated with this regimen [11, 33]. Only 2% of patients experienced grade 3 or 4 bleeding events. The risk for hematologic toxicity was higher with higher baseline bone marrow involvement with NHL. It was concluded that the safety profile of single-dose $^{90}$Y-ibritumomab tiuxetan RIT is appropriate in patients with relapsed NHL and $^{90}$Y-ibritumomab tiuxetan, although contact with the patient’s bodily fluids should be avoided [11]. AEs such as hair loss, nausea and vomiting, cardiotoxicity, nephrotoxicity, and neurotoxicity, associated with systemic chemotherapies for the treatment of NHL, are not associated with RIT using $^{90}$Y-ibritumomab tiuxetan [11].

Although patient management strategies differ depending on the properties attributed to the radiolabeled nucleotide, the efficacy of the two RIT agents remains consistent. The radioimmunoconjugate $^{131}$I-tositumomab is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed NHL, including patients with rituximab-refractory NHL. A study of $^{131}$I-tositumomab in 59 patients with relapsed or refractory B-cell NHL showed an ORR of 83% in patients with low-grade or

<table>
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<th>Table 1. (Continued)</th>
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<tr>
<td><strong>Properties</strong></td>
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<tr>
<td>Contraindicated for use in pregnancy</td>
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<tr>
<td>Subsequent therapy</td>
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*Median duration of response; †Median time to progression.*
transformed NHL and 43% in patients with aggressive NHL [34]. The median progression-free survival (PFS) time was 12 months for responders and 20.3 months for complete responders. A further trial of tositumomab and 131I-tositumomab in 40 patients with indolent (5%), follicular (70%), or transformed B-cell (25%) lymphoma, progressive after rituximab therapy, gave a confirmed ORR of 65% and CR rate of 38%, which were not significantly associated with prior response to rituximab [35]. After a median follow-up of 3.3 years, the median PFS time was 24.5 months for responders, compared with 10.4 months overall. Furthermore, the median PFS time was not reached for patients who experienced a CR. Although 50% of patients experienced transient grade 3–4 marrow toxicity, the regimen was generally well tolerated.

A pivotal registration trial of 131I-tositumomab in 60 heavily pretreated (but rituximab-naïve) patients with low-grade (60%) or transformed (38%) lymphoma showed a response rate of 65% and an acceptable safety profile [36]. Compared with the last qualifying chemotherapy regimens, the comparator in this trial, 131I-tositumomab, was associated with a significantly greater median duration of response (3.4 months versus 6.5 months; \( p < .001 \)), and in the small subset of patients with a CR (20%), the median duration of response had not been reached after a median follow-up of 47 months. In a trial of 131I-tositumomab in patients with previously untreated FL, 95% of the patients responded to therapy, with a CR rate of 75% [37]. After a median follow-up of 8 years, the overall 8-year PFS rate was 50%, compared with 64% for patients who achieved a CR [38]. Hematologic toxicity was common in the study, but usually of moderate intensity [39].

**RIT Consolidation After First Remission**

Recently, the European label for 90Y ibritumomab tiuxetan was expanded to include consolidation therapy after remission induction in previously untreated patients with FL. The updated indication was based on new data from a randomized phase III study of consolidation with 90Y-ibritumomab tiuxetan after first-line induction chemotherapy in patients with advanced-stage FL. Although many randomized controlled trials of rituximab added to chemotherapy in the treatment of NHL have since been published documenting superior outcomes associated with the addition of rituximab [40], this trial was designed prior to the widespread use of rituximab plus chemotherapy for FL. Therefore, patients generally received first-line induction chemotherapy without rituximab in most cases. Although a few patients did receive rituximab plus chemotherapy (15.6% in the control arm and 13.2% in the consolidation arm), the impact of consolidating more aggressive induction therapy (rituximab plus chemotherapy) cannot currently be compared. However, follow-up is ongoing in these patients. Results from this trial showed a >2 years longer PFS duration and an unprecedented rate of conversion from partial response (PR) to CR as a result of consolidation with 90Y-ibritumomab tiuxetan [41, 42]. Patients who had previously achieved a CR or PR following first-line induction therapy (\( n = 409 \)) were randomized to receive either consolidation (rituximab, 250 mg/m² on day -7 and day 0 plus 90Y-ibritumomab tiuxetan, 14.8 MBq/kg on day 0; \( n = 202 \)) or no further therapy (\( n = 207 \)). A significantly prolonged PFS time was observed with consolidation than with control therapy (54 versus 14 months; \( p = .0001 \)), regardless of whether patients achieved a PR (29.6 versus 6.7 months; \( p = .001 \)) or CR/unconfirmed CR (\( >67 \) versus 30.5 months; \( p = .015 \)) after induction treatment [42]. Of the patients who achieved a PR after induction treatment, 77% were converted to CR/unconfirmed CR after consolidation treatment, with a final CR rate of 87% [41]. Because the median OS duration for FL is typically 8–10 years [43, 44], it is not surprising that no significant difference in terms of OS has yet emerged between the two treatment groups. The tolerability profile was similar to that observed in the previous trials, with no unexpected toxicities [41].

Consolidation with 131I-tositumomab therapy following CHOP chemotherapy was also studied in 60 patients with previously untreated advanced FL [45, 46]. With an ORR of 91%, including a 69% CR rate and a 57% conversion rate from non-CR following RIT, the estimated 5-year OS rate was 87%, whereas the estimated 5-year PFS rate was 67% [46]. In a further phase II study in 30 patients with previously untreated FL, CVP chemotherapy resulted in an ORR of 100% (CR rate, 50%), and following consolidation with 131I-tositumomab RIT, a further 30% achieved a CR [47]. For further information regarding the use of RIT consolidation therapy, see Morschhauser et al. [48].

There is also significant clinical interest in the use of rituximab maintenance following induction therapy for FL. A recent meta-analysis regarding the use of rituximab maintenance for the treatment of patients with FL showed a survival benefit in patients with refractory or relapsed FL, although no clear benefit was observed in previously untreated patients [49]. Data from thePrimary Rituximab and Maintenance (PRIMA) study, of first-line rituximab plus chemotherapy with or without rituximab maintenance in patients with advanced FL, are eagerly awaited to clarify this [50]. Once the role of rituximab maintenance has been ascertained, the potential use of rituximab maintenance following RIT consolidation should also be assessed. To date, one trial of 20 previously untreated patients with FL receiving chemotherapy and RIT induction with 90Y-ibritu-
omab tiuxetan followed by rituximab maintenance has shown encouraging response rates, although longer follow-up is needed to evaluate any survival benefit [51].

In order to learn more about real-life patients receiving RIT outside the clinical trial setting, the international RIT network was launched in 2006 to collect data from many countries. By January 2008, 579 patients had been entered [52]. As expected, the majority of patients in this database have FL (62%); however, patients with diffuse large B-cell lymphoma (15%) and mantle cell lymphoma (12%) are also receiving RIT in real-life clinical practice. We await further analyses of outcomes and toxicity with interest, because these will further help to guide new clinical trials and clinical practice.

**ADMINISTRATION OF RIT**

Prior to treatment with 90Y-ibritumomab tiuxetan, patients receive rituximab as an unlabeled pretreatment antibody on day 1 of the therapeutic regimen. The use of rituximab as a pretreatment antibody increases radioantibody biodistribution by binding to the CD20 antigen on “non-specific” binding sites such as circulating and splenic B cells, thus enhancing tumor targeting [11].

As part of the RIT regimen in the U.S. and Switzerland, a 5-mCi (185-MBq) injection of 111In-labeled ibritumomab tiuxetan is administered prior to 90Y-ibritumomab tiuxetan to assess biodistribution before the therapeutic dose. This occurs 4 hours after the 250-mg/m² infusion of rituximab. A visual evaluation of whole-body, planar-view, anterior, and posterior gamma images are then performed at 2–24 hours (scan 1) and 48–72 hours (scan 2) after injection of the imaging dose [11]. If there are any ambiguities, a third scan can be performed at 90–120 hours [23, 24, 53].

It is expected that, in the first scan, RIT will be easily detectable in the blood pool areas, but this will become less in later images. Low uptake is expected in the lungs, kidneys, and urinary bladder, with higher uptake expected in the normal liver and spleen [11]. Visualization of the tumor is not a criterion for proceeding to the active therapy, although if the images reveal altered biodistribution, the patient will not receive the therapeutic dose. Altered biodistribution includes a failure to visualize the blood pool on the first image, which possibly indicates rapid clearance of the radionuclide, or diffuse uptake in the normal lungs or kidneys becoming more intense in the liver on the second or third image [11].

Data from phase I and II clinical trials were used to determine the optimal therapeutic dose of 90Y-ibritumomab tiuxetan, and the nonmyeloablative MTD was identified as 0.4 mCi/kg (15 MBq/kg), to a maximum of 32 mCi (1.2 GBq), in patients with baseline platelet counts ≥150,000/μl [11, 29]. The therapeutic dose is adjusted to 0.3 mCi/kg (11 MBq/kg), to a maximum of 32 mCi (1.2 GBq), for patients with mild thrombocytopenia at baseline (platelet count, 100,000–149,000/μl), because baseline thrombocytopenia indicates reduced marrow reserves and can indicate severe cytopenia [11, 29, 32, 54, 55]. Therapeutic injections of 90Y-ibritumomab tiuxetan are administered on days 7–9 of the regimen, along with a second infusion of rituximab (250 mg/m²) [11].

Dosimetry studies have been used to estimate the radiation-absorbed doses by individual organs, helping to determine whether a patient can be treated safely, and by the tumor, helping to predict the therapeutic value of RIT. Estimates of radiation-absorbed doses were obtained using blood sampling data and quantitative imaging with 111In-ibritumomab tiuxetan [11, 56–61]. These studies found that the estimated radiation-absorbed doses to normal organs are substantially below recognized upper safety limits (<2,000 cGy for normal organs and <300 cGy for red marrow) and do not correlate with hematologic toxicity [60]. Therefore, dosimetric calculations are not mandatory for all patients [4].

**SELECTING PATIENTS FOR RIT**

A number of clinical criteria should be considered when assessing the suitability of patients for RIT, which is critical to ensure that the efficacy and safety of RIT are optimized [62]. Prior hypersensitivities to murine antibodies or other components of the regimen, such as rituximab, yttrium chloride, or tositumomab, are contraindications for RIT, as are bone marrow transplants [4]. Although the use of RIT is also contraindicated in patients who have had prior stem cell transplants because of the higher increased risk for hematologic complications potentially associated with compromised bone marrow function, preliminary studies indicate that RIT at a reduced dose may be well tolerated with potential efficacy benefit for patients who relapse following stem cell transplants, although further study is needed to verify this [63–65]. Because of the risk for hematologic toxicity, RIT is also contraindicated in patients whose: platelet count is <100,000/µl and/or neutrophil count is <1.5 × 10³/µl; bone marrow exhibits hypocellularity (<15%), reduction in bone marrow precursors, or a history of failed stem cell collection; or lymphoma cells comprise ≥25% of the bone marrow [4, 62, 66]. However, patients with mild thrombocytopenia (platelet count, 100,000–149,000/μl) can receive a reduced dose of 90Y-ibritumomab tiuxetan [33]. A recent meta-analysis demonstrated that the response rate, duration of response, and safety profile of 90Y-ibritumomab tiuxetan in elderly patients (≥70 years) were similar to those of younger pa-
tients [67]. Therefore, elderly patients with comorbid conditions are ideal candidates for RIT. Indeed, in the RIT patient registry, the highest proportion of patients was in the 60- to <70-year age group, and >64 patients aged >70 years had received RIT.

Response to 90Y-ibritumomab tiuxetan has been observed in patients with both good and poor prognostic factors, and good candidates for treatment include patients with compromised performance status or high-risk International Prognostic Index, high serum lactate dehydrogenase, and disease resistant to prior chemotherapy or radiotherapy regimens [30, 33, 62, 68]. Because bulky disease (>10 cm) is less responsive to RIT, chemotherapy is often used to debulk the disease prior to treatment. Furthermore, obesity is not a contraindication. A checklist of factors to consider when selecting patients for RIT with 90Y-ibritumomab tiuxetan is given in Figure 2.

The Follicular Lymphoma International Prognostic Index (FLIPI) to define patients as low, intermediate, or high risk is outlined in Table 2 and is useful for evaluating patients and determining the most appropriate treatments [69]. FLIPI is widely used in the U.S. and Europe to guide treatment decisions, and patients in all risk categories could be suitable for RIT, although some patients may benefit more than others. Indeed, although all patients in the randomized phase III First-line Indolent Trial showed a PFS benefit with RIT consolidation regardless of FLIPI category, patients in the FLIPI intermediate-risk category expe-

### Table 2. Follicular Lymphoma International Prognostic Index scores [68]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>High risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;60 years</td>
<td>≤60 years</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td>III–IV</td>
<td>I–II</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>&lt;120 g/l</td>
<td>≥120 g/l</td>
</tr>
<tr>
<td>Number of modal sites</td>
<td>&gt;4</td>
<td>≤4</td>
</tr>
<tr>
<td>Serum lactate dehydrogenase level</td>
<td>&gt;normal</td>
<td>≤normal</td>
</tr>
</tbody>
</table>

Three risk groups have been defined according to the number of parameters in the high-risk category that the patient falls into:

- **low risk** (0–1 adverse factor).
- **intermediate risk** (2 factors).
- **poor risk** (≥3 factors).

![Figure 2. Checklist for selecting patients for radioimmunotherapy.](image-url)
rienced a significantly longer PFS time (53.9 versus 11.3 months; \( p < .0001 \)) [41].

**INDIVIDUAL TREATMENT STRATEGIES FOR PATIENTS WITH ADVANCED FL**

Although a wide variety of patients are eligible for RIT with \(^{90}\)Y-ibritumomab tiuxetan, different treatment strategies could be used to optimize results. Patients with a good performance/functional status, good organ function, good life expectancy, few comorbidities, high tumor burden, intermediate/high FLIPI score, and a low risk for toxicity can be classed as medically “fit.” It is feasible to aim to achieve a cure in such patients using a more aggressive therapeutic strategy that will maximize responses and minimize the level of residual disease. Therefore, it may be possible to treat such patients with an induction regimen consisting of high-dose immunochemotherapy followed by consolidation of remission with RIT, and then maintain the maximum response achieved with induction and consolidation with a rituximab maintenance regimen. Trials are currently under way to evaluate such a regimen. However, preliminary data on such an approach were recently published by Jacobs et al. [70], with a three-cycle R-CHOP induction regimen followed by consolidation and four cycles of maintenance. The optimal maintenance schedule is still to be defined and the benefit of adding rituximab maintenance after a first-line rituximab-based combination is currently being investigated in a large phase III trial.

“Compromised” patients can be classed as those with lower organ function and performance status, a medium life expectancy, more comorbidities, and a higher risk for toxicity. These patients would benefit from less intensive therapy aimed at reducing the burden of lymphoma, such as a regimen including induction treatment with R-CHOP immunochemotherapy (4 weeks of rituximab, 375 mg/m\(^2\) weekly infusions, followed by three cycles of standard R-CHOP) and consolidation with RIT [71] or three cycles of standard R-CHOP before RIT, followed by four weekly 375-mg/m\(^2\) rituximab treatments as consolidation therapy [70].

“Frail” patients, or those with severely compromised or-
gan function and performance status, low life expectancy, many comorbidities, and a high risk for toxicity, would be better suited to a more “supportive” regimen aimed at controlling symptoms. There are currently some preliminary data suggesting that another option to limit toxicity could be to treat with RIT alone, without induction chemotherapy, because RIT has a very manageable tolerability profile and is not associated with much of the toxicity attributed to the intensive chemotherapy regimen [72].

The overall aim of developing patient classifications in

**Figure 4.** Patient X scans.

Abbreviations: CT, computed tomography; LAD, lymphadenopathy; PET, positron emission tomography; RIT, radioimmunotherapy.
REFERENCES


7 Marcus R, Imrie K, Belch A et al. CVP chemotherapy plus rituximab com...


42 Morschhauser F, Bischof-Delaloye A, Rohatiner AZS et al. Extended follow-up of the international randomized phase 3 First-line Indolent Trial (FIT) shows durable benefit of 90Y-ibritumomab tiuxetan (Zevalin®) con-
Radioimmunotherapy for NHL Patients


64 Shimoni A, Zwas ST, Oksman Y et al. Ibritumomab tiuxetan (Zevalin) combined with reduced-intensity conditioning and allogeneic stem-cell transplantation (SCT) in patients with chemorefractory non-Hodgkin’s lymphoma. Bone Marrow Transplant 2008;41:355–361.


