Administration Guidelines for Radioimmunotherapy of Non-Hodgkin’s Lymphoma with $^{90}$Y-Labeled Anti-CD20 Monoclonal Antibody

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$^{90}$Y-ibritumomab tiuxetan is a novel radioimmunotherapeutic agent recently approved for the treatment of relapsed or refractory low-grade, follicular, or CD20$^+$ transformed non-Hodgkin’s lymphoma (NHL). $^{90}$Y-ibritumomab tiuxetan consists of a murine monoclonal antibody covalently attached to a metal chelator, which stably chelates $^{111}$In for imaging and $^{90}$Y for therapy. Both health care workers and patients receiving this therapy need to become familiar with how it differs from conventional chemotherapy and what, if any, safety precautions are necessary. Because $^{90}$Y is a pure $\beta$-emitter, the requisite safety precautions are not overly burdensome for health care workers or for patients and their families. $^{90}$Y-ibritumomab tiuxetan is dosed on the basis of the patient’s body weight and baseline platelet count; dosimetry is not required for determining the therapeutic dose in patients meeting eligibility criteria similar to those used in clinical trials, such as $\leq$25% lymphomatous involvement of the bone marrow. $^{111}$In- and $^{90}$Y-ibritumomab tiuxetan are labeled at commercial radiopharmacies and delivered for on-site dose preparation and administration. Plastic and acrylic materials are appropriate for shielding during dose preparation and administration; primary lead shielding should be avoided because of the potential exposure risk from bremsstrahlung. Because there are no penetrating $\gamma$-emissions associated with the therapy, $^{90}$Y-ibritumomab tiuxetan is routinely administered on an outpatient basis. Furthermore, the risk of radiation exposure to patients’ family members has been shown to be in the range of background radiation, even without restrictions on contact. There is therefore no need to determine activity limits or dose rate limits before patients who have been treated with $^{90}$Y radioimmunotherapy are released, as is necessary with patients who have been treated with radiopharmaceuticals that contain $^{131}$I. Standard universal precautions for handling body fluids are recommended for health care workers and patients and their family members after $^{90}$Y-ibritumomab tiuxetan administration. In summary, $^{90}$Y-ibritumomab tiuxetan introduces $^{90}$Y into clinical practice and expands the role nuclear medicine plays in the care of patients with cancer. Understanding the unique properties of this novel radioimmunoconjugate will facilitate its safe and effective use.

Key Words: radioimmunotherapy; non-Hodgkin’s lymphoma; $^{90}$Y-ibritumomab tiuxetan; anti-CD20 monoclonal antibodies; guidelines


Anti-CD20 monoclonal antibodies labeled with $^{90}$Y are novel radioimmunotherapeutic agents that are being investigated for the treatment of non-Hodgkin’s lymphoma (NHL) and other hematologic malignancies. One such agent, $^{90}$Y-ibritumomab tiuxetan (Zevalin; IDEC Pharmaceuticals Corp., San Diego, CA), has been extensively investigated in relapsed or refractory low-grade, follicular, or CD20$^+$ transformed NHL and has recently received U.S. Food and Drug Administration approval for commercialization. This agent consists of ibritumomab, the parent murine monoclonal antibody from which the widely used rituximab (Rituxan; IDEC Pharmaceuticals) was developed, and tiuxetan, which stably chelates $^{111}$In for imaging and $^{90}$Y for therapy. The safety and efficacy of $^{90}$Y-ibritumomab tiuxetan in the treatment of NHL have been described in detail elsewhere. Briefly, using International Workshop response criteria for NHL, $^{90}$Y-ibritumomab tiuxetan has produced response rates of 74%–83% in patients with relapsed or refractory low-grade, follicular, or CD20$^+$ transformed NHL, including an impressive 83% response rate in a clinical trial conducted on patients for whom prior rituximab therapy had failed ($^1$–$^4$). Nuclear medicine professionals will be important members of the multidisciplinary teams.
that are necessary to administer this agent. In this review, we recommend administration guidelines for \(^{90}\)Y radioimmunotherapy.

Radionuclide therapy involves administering radioactive materials, often \(\beta\)-emitters, to deliver therapeutic doses of radiation to specific targets within the patient. An underlying premise in this review is that all physicians, nurses, technologists, and other health care workers who are involved before, during, and after the use of \(^{90}\)Y radioimmunotherapy must be familiar with the safety measures it entails. Patients should also understand how this treatment differs from conventional chemotherapy and what safety measures are necessary to prevent radiation exposure to others. It is incumbent on nuclear medicine physicians and other health care workers to explain these new treatments and their safety precautions to their patients so that they can be treated in the safest manner possible. The radiation safety requirements with \(^{90}\)Y, a pure \(\beta\)-emitter, are not overly cumbersome for either health care providers or patients.

**RADIOIMMUNOTHERAPY WITH \(^{90}\)Y**

**Physical Characteristics of \(^{90}\)Y**

\(^{90}\)Y is a pure \(\beta\)-emitter with a half-life of 64 h (2.7 d) that decays to \(^{90}\)Zr. It has high \(\beta\)-energy and an effective path-length of 5.3 mm, meaning that 90% of its energy is absorbed within a sphere with a 5.3-mm radius (5). This pathlength corresponds to 100–200 cell diameters, giving \(^{90}\)Y a broad crossfire effect when it is conjugated to a monoclonal antibody such as ibritumomab (Table 1) (6,7).

**TABLE 1**

Features of \(^{90}\)Y-Ibritumomab Tiuxetan Regimen for Non-Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th>Category</th>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody</td>
<td>IgG1 (k) murine monoclonal antibody</td>
</tr>
<tr>
<td>Stability of immunoconjugate</td>
<td>Stable urea-type bond</td>
</tr>
<tr>
<td>Antibody used before therapeutic dose to enhance biodistribution</td>
<td>Rituximab (chimeric)</td>
</tr>
<tr>
<td>Effective blood half-life</td>
<td>Mean, 27 h (range, 14–44 h)</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>7.3% ± 3.2% over 7 d</td>
</tr>
<tr>
<td>Dosimetry</td>
<td>Not necessary for approved indication: (^{111})In-ibritumomab tiuxetan used as surrogate in imaging performed to confirm expected biodistribution as additional safety measure</td>
</tr>
<tr>
<td>Administration</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>8 d</td>
</tr>
<tr>
<td>Development of human antimouse or human antichimeric antibodies</td>
<td>1%–2% of patients</td>
</tr>
</tbody>
</table>

Features are from Wiseman et al. (6) and Zelenetz (7).

This crossfire effect is postulated to increase tumor killing beyond that of nonradiolabeled antibodies, by irradiating tumor cells that are not bound to the antibody. This effect may be particularly beneficial in patients with bulky tumors or tumors that are poorly vascularized.

**Dosimetry and Dosing**

The therapeutic index of a radionuclide is the ratio of the radiation absorbed dose delivered to cancerous cells and the dose delivered to normal tissues. Dosimetry was performed in the clinical trials of \(^{90}\)Y-ibritumomab tiuxetan to determine its therapeutic index and ensure that the radiation exposure to healthy organs and the red marrow was well within acceptable limits (8).

Dosimetry was initially an important component of therapy with \(^{90}\)Y-ibritumomab tiuxetan in patients with low-grade NHL. The researchers sought to determine whether it was necessary or helpful to measure the organ-specific accumulation of a radiotherapeutic surrogate in each patient before treatment with \(^{90}\)Y-ibritumomab tiuxetan. A tracer dose of ibritumomab labeled with \(^{111}\)In, which emits \(\gamma\)-radiation, was used as an imaging agent to predict the distribution within the body of the subsequent therapeutic dose of \(^{90}\)Y-ibritumomab tiuxetan. Preclinical studies had shown that the biodistribution of \(^{90}\)Y-ibritumomab tiuxetan, assessed by direct determination of the presence of \(^{90}\)Y, is in fact predicted by the biodistribution of the \(^{111}\)In-labeled antibody (9).

Wiseman et al. (10) have evaluated the estimated dose to solid organs and the marrow after the administration of a tracer dose of \(^{111}\)In-ibritumomab tiuxetan in a phase 1–2 clinical trial. Patients with histologically confirmed relapsed or refractory low-grade, intermediate-grade, or mantle cell NHL in whom chemotherapy had failed and in whom there was no more than 25% involvement of the bone marrow space (as determined by bone biopsy) were eligible for the trial. Quantitative gamma camera imaging, serial blood sampling, and MIRDOS3 software (Radiation Internal Dose Information Center, Oak Ridge, TN) were used to estimate the radiation absorbed doses before treatment with \(^{90}\)Y-ibritumomab tiuxetan. The radiation absorbed doses to normal organ and the marrow were within the specified upper limits of 20 Gy for solid organs and 3 Gy for red marrow in all 56 patients in the study. The median estimated radiation absorbed dose to tumor was 17 Gy (range, 5.8–67 Gy). The tumor–to–normal organ (i.e., the normal organ with the highest radiation absorbed dose) ratio was 7:1. Because of the acceptable radiation absorbed doses to normal solid organs and the marrow, it was possible to give the therapeutic \(^{90}\)Y-ibritumomab tiuxetan dose in all patients. Furthermore, the estimated radiation absorbed dose to the red marrow did not correlate with hematotoxicity manifested as transient thrombocytopenia, neutropenia, or anemia. These findings indicate that, although the primary toxicity of therapy with \(^{90}\)Y-ibritumomab tiuxetan is hematologic, such toxicity in this population of heavily pretreated
patients with NHL could be predicted not by dosimetry but by the patients’ bone marrow reserves.

Additional dosimetry results in 72 patients who were treated with $^{90}$Y-ibritumomab tiuxetan in a phase 3 clinical trial confirmed the initial results in the phase 1–2 study (Fig. 1) (11). Further analyses of these data found no significant correlations between the grade of hematologic toxicity and pharmacokinetic or dosimetric parameters, including whole-blood half-life, whole-blood residence time, red marrow radiation dose (blood- and image-derived), and total body dose (Table 2) (11).

On the basis of the dosimetry results and the results in dosing based on patient body weight and platelet count, investigators have concluded that $^{90}$Y-ibritumomab tiuxetan can be safely used in doses based on patient body weight and pretreatment platelet counts (14.8 MBq/kg [0.4 mCi/kg] in patients with platelet counts of $150 \times 10^9$ to $299 \times 10^9$/$L$, and 11.1 MBq/kg [0.3 mCi/kg] in patients with counts of $100 \times 10^9$ to $149 \times 10^9$/$L$). Dosimetry was not necessary in the cohort of patients in the clinical trials who met the criteria for pretreatment platelet count and percentage of marrow involvement with lymphoma (<25% as determined by bone marrow biopsy), and clinical trials without dosimetry in such patients are ongoing. Dosimetry should be performed, however, when $^{90}$Y-ibritumomab tiuxetan is used as an investigational treatment in indications (e.g., in the myeloablative setting) different from the one defined in the registration trials in patients with low-grade NHL. Imaging with $^{111}$In-ibritumomab tiuxetan is performed to confirm the expected biodistribution as an additional safety measure before administering the therapeutic dose of $^{90}$Y-ibritumomab tiuxetan.

It should also be noted that pharmacokinetic studies have shown that almost the entire radioactivity in the therapeutic dose of $^{90}$Y-ibritumomab tiuxetan is retained within the body. Urinary excretion is the primary clearance mechanism, and it accounts for the elimination of only 7.3% ± 3.2% of the administered dose over 7 d (12).

### TABLE 2
Lack of Correlation Between Hematologic Toxicity Grade and Pharmacokinetic and Dosimetric Measures in Phase 3 Trial of $^{90}$Y-Ibritumomab Tiuxetan ($n = 72$)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Grade of hematologic toxicity (nadir)</th>
<th>0–2</th>
<th>3</th>
<th>4</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood half-life (h)</td>
<td>Neutropenia</td>
<td>27</td>
<td>30</td>
<td>27</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>27</td>
<td>28</td>
<td>29</td>
<td>0.38</td>
</tr>
<tr>
<td>Blood residence time (h)</td>
<td>Neutropenia</td>
<td>25</td>
<td>30</td>
<td>27</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>27</td>
<td>26</td>
<td>23</td>
<td>0.95</td>
</tr>
<tr>
<td>Blood-derived RM dose (Gy)</td>
<td>Neutropenia</td>
<td>0.66</td>
<td>0.82</td>
<td>0.70</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>0.69</td>
<td>0.71</td>
<td>0.59</td>
<td>0.80</td>
</tr>
<tr>
<td>Image-derived RM dose (Gy)</td>
<td>Neutropenia</td>
<td>1.02</td>
<td>1.15</td>
<td>1.16</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>1.01</td>
<td>1.10</td>
<td>1.32</td>
<td>0.26</td>
</tr>
<tr>
<td>Total body dose (cGy)</td>
<td>Neutropenia</td>
<td>0.59</td>
<td>0.61</td>
<td>0.22</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>0.58</td>
<td>0.61</td>
<td>0.57</td>
<td>0.13</td>
</tr>
</tbody>
</table>

RM = red marrow.

Data are from Wiseman et al. (11).


Materials with a low atomic number, such as plastic or acrylics, make ideal shields for preparing the drug. The β-particles are completely absorbed in approximately 1 cm of these materials. In addition, bremsstrahlung production is proportional to the atomic number (or the effective atomic number for compounds), which is low for these materials (14,15). For comparison, the effective Z of polyethylene is 5.9; of acrylic, 7.5; and of water, 7.9. In the case of 90Y, the percentage of the total β-energy that is converted to bremsstrahlung when it passes through a material with a Z of 7.9 is only 0.6%. Geiger–Müller survey counters are extremely efficient for detecting these low-energy photons but could give erroneously high readings unless they have been calibrated for 90Y bremsstrahlung. Syringe shields made of materials such as acrylic are preferred over conventional shields made with lead or leaded glass for use during radiolabeling and preparation. If lead is used, the higher-energy bremsstrahlung produced will necessitate thicker shielding than is commonly used.

Before 90Y-ibritumomab tiuxetan is released from the nuclear pharmacy, it must be tested for radiochemical purity, to assess the percentage of 90Y that has been chelated by the antibody–tiuxetan complex. A commercial kit for instant thin-layer chromatography can be used. The test is performed in triplicate and the results are averaged. The radioimmunoconjugate can be released for patient administration if its radiochemical purity is ≥95%. When the drug is administered, it should also be shielded as described above. In addition to the 1 cm of plastic surrounding the syringe, lead (or more plastic) can be used for shielding the low-energy bremsstrahlung.

90Y-ibritumomab tiuxetan is administered as a slow intravenous push over approximately 10 min. The drug should not be given as a rapid intravenous bolus. As shown in Table 1, therapy with 90Y-ibritumomab tiuxetan is preceded by a dose of rituximab, which is administered to enhance the biodistribution of the subsequent radiolabeled antibody by blocking readily accessible CD20 sites in the peripheral blood and preventing indiscriminate uptake of the radiolabeled antibody in the reticuloendothelial system (7). As such, rituximab is given at a dose of 250 mg/m² by slow intravenous infusion. Ideally, 90Y-ibritumomab tiuxetan should be administered within 4 h of completion of the rituximab dose (16).

The most common nonhematologic adverse events reported during clinical trials of 90Y-ibritumomab tiuxetan included, but were not limited to, asthenia, nausea, infection, chills, fever, and abdominal pain. Because of the potential for anaphylactic and other hypersensitivity reactions related to the administration of proteins to patients, medications for the treatment of such reactions, such as epinephrine, antihistamines, and corticosteroids, should be readily available during the administration of both rituximab and 90Y-ibritumomab tiuxetan.

Precautions After 90Y Administration

90Y-ibritumomab tiuxetan can be routinely administered on an outpatient basis. Treatment with 90Y-labeled antibodies results in the emission of β-radiation and low-level bremsstrahlung radiation, but there is no emission of penetrating γ-radiation, as there is with radiopharmaceuticals that contain 131I, for example. Because no penetrating γ-waves are produced during treatment with 90Y, there is minimal risk of radiation exposure to health care workers or to patients’ family members and others with whom they have contact. Patients can be released immediately after treatment, in accordance with the guidelines in Nuclear Regulatory Commission (NRC) Regulatory Guide 8.39, corresponding to Title 10 Code of Federal Regulations, parts 20 and 35 (17,18). Because of the minimal risk of exposure to other persons, there is no need to determine activity limits or dose rate limits before patients who have been treated with 90Y radioimmunotherapy are released, as is necessary with patients who have been treated with radiopharmaceuticals that contain 131I.

The radiation exposure to persons with whom a patient treated with 90Y radioimmunotherapy has contact can be calculated. The specific bremsstrahlung constant for 90Y in soft tissue in a 70-kg patient is 1.52 μGy · cm²/MBq · h (19). The NRC guidelines require inpatient stays for patients from whom radiation exposure to others is likely to exceed 5 mSv (500 mrem). Assuming some absorption of the bremsstrahlung by the patient, an inpatient stay for a patient treated with 90Y-ibritumomab tiuxetan would be required only if activities > 4,180 GBq (113,000 mCi) were administered. Even with radiation absorption by the patient’s body disregarded, the administered dose would have to be at least 1,425 GBq (38,500 mCi) for the outpatient exposure limit of 5 mSv (500 mrem) to be exceeded. Because the typical patient dose of 90Y-ibritumomab tiuxetan is at least a thousandfold less than this (777–1,110 MBq [21–30 mCi]), the NRC requirements for outpatient treatment will always be met.

Furthermore, in a study to quantify the radiation risks to family members with unrestricted contact with patients who had been treated with 90Y-ibritumomab tiuxetan, it was determined that radiation exposure in the first week after treatment is very low, in the range of background radiation (20). The patients in this study were not isolated from their family members, nor was any type of patient shielding used. The only recommendations to the family were to avoid contamination from body fluids (saliva, blood, urine, stool). The family member with closest contact to the patient wore a DoseGUARD Plus personal electronic dosimeter (AEA Technology QSA, Inc., Burlington, MA) for the first 7 d after treatment with 90Y-ibritumomab tiuxetan. The median deep dose equivalent radiation exposure was a total accumulation of 0.035 mSv over the 7-d period (range, 0.014–0.077 mSv), which is within the range of what might be expected from normal background radiation. The standard
CONCLUSION

90Y radioimmunotherapy combines the targeting benefits of a monoclonal antibody with the efficacy of radiation in the treatment of NHL, an exquisitely radiosensitive hematologic malignancy. Advances in radioimmunotherapy are increasing the role that nuclear medicine professionals play in the treatment of patients with cancer. 90Y-ibritumomab tiuxetan introduces 90Y into clinical medicine, and understanding this radionuclide and how it can safely be handled and used is necessary. Because 90Y is a pure β-emitter, radiation safety precautions for caregivers and patients after treatment are minimal.

Because of the low risk of radiation exposure to other persons from patients who have been treated with 90Y radioimmunotherapy, this treatment can be safely administered on an outpatient basis, with minimal or no disruption to patients’ daily routines. Dosimetry calculations have been found to be unnecessary for determining the dose of 90Y-ibritumomab tiuxetan in patients with low-grade NHL; body weight and platelet count are all that is required in patients who meet the criteria of <25% bone marrow involvement (as measured by bone biopsy). Patients with low-grade NHL who meet the criteria established in the registration trials of 90Y-ibritumomab tiuxetan can safely receive a standard weight-based dose. Dosimetry should, however, be performed for investigational use of this agent in other indications. Because only patients with NHL involvement of <25% of intratrabecular bone marrow space have been treated in clinical trials, the role of dosimetry in patients with greater bone marrow involvement is not known. This new approach to the treatment of relapsed or refractory low-grade, follicular, or CD20+ transformed NHL presents an opportunity for a greater multidisciplinary approach to patient care, and it gives patients a new option that compares favorably with the currently available chemotherapeutic options.

REFERENCES


triad of precautions against radiation exposure—minimizing the duration of exposure, maximizing distance from the source, and using shielding—are therefore not necessary with patients who have been treated with 90Y radioimmunotherapy. Standard universal precautions to avoid contact with body fluids are all that are required.

Another consideration in radiation safety precautions for patients treated with 90Y-ibritumomab tiuxetan is the pharmacokinetic profile. The median effective half-life of 90Y-ibritumomab tiuxetan in the blood in clinical trials was 27 h (range, 14–44 h) (9). As was noted above, urinary excretion is the main route of elimination, as determined by the correlation of urinary-excretion and whole-body-retention data (12). Urinary excretion has been reported as 7.3% ± 3.2% over 7 d (12). Assuming a urinary excretion of 7.3% over a week and a maximum dose of 1,184 MBq (32 mCi), the total urinary excretion in that period would be 85 MBq (2.3 mCi). The activity per urination would be in kilobecquerels (microcuries), making this an unlikely source of exposure. Even if the radioactive compound were swallowed (e.g., in food that had been contaminated by contaminated hands), it would be transported through the gastrointestinal tract and not be absorbed (21). Ordinary amounts of blood, such as through menstruation, a severe laceration, or hemorrhoids, will not contain appreciable radioactivity. The recommended release instructions for patients who have been treated with 90Y-ibritumomab tiuxetan are given in Table 3.

Some patients may be treated with 90Y-ibritumomab tiuxetan as inpatients, not because of any radiation risk to others, but because it is medically required. Medical personnel handling blood or urine routinely wear gloves that would absorb the small amount of radiation that might be present and take other measures to avoid contact with these body fluids. In addition, the bags, vials, and tubes that are normally used to contain these fluids in the hospital would also absorb any radiation that might be present, making contamination of personnel highly unlikely. No additional special precautions beyond the standard universal precautions already in place are therefore necessary for hospital caregivers of inpatients treated with 90Y-ibritumomab tiuxetan.

### TABLE 3
Recommended Patient Release Instructions After Treatment with 90Y-Ibritumomab Tiuxetan

<table>
<thead>
<tr>
<th>Interval after treatment</th>
<th>Recommended instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 d</td>
<td>Clean up spilled urine and dispose of any body fluid–contaminated material to prevent its being handled (e.g., flush it down toilet or place it in plastic bag in household trash)</td>
</tr>
<tr>
<td>1 wk</td>
<td>Wash hands thoroughly after using toilet</td>
</tr>
<tr>
<td></td>
<td>Use condoms for sexual relations</td>
</tr>
</tbody>
</table>

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