Techniques for Using Bexxar for the Treatment of Non-Hodgkin’s Lymphoma*

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**Objective:** This article briefly describes the concept of radioimmunotherapy and treatment of non-Hodgkin’s lymphoma by a new radiopharmaceutical that uses this technique. The rationale for such an approach is reviewed, and some of the practical consequences for technologists are examined. These include the idea of performing individually customized dosimetry and using relatively high $^{131}$I doses on an outpatient basis. After reading this article, the nuclear medicine technologist should be able to (a) describe radioimmunotherapy and its advantages, (b) explain why treatment of non-Hodgkin’s lymphoma is enhanced by this technique, (c) understand the role of the predose study and its use in determining the therapeutic dose, and (d) recognize the radiation safety issues involved with the therapeutic dose administration and patient release criteria.

**Key Words:** $^{131}$I; radioimmunotherapy; monoclonal antibodies; lymphoma


The use of radiopharmaceuticals for therapeutic purposes dates back to the dawn of nuclear medicine >50 y ago (1). The clinical use of radiolabeled monoclonal antibodies is much more recent, despite several decades of investigational studies (2). These 2 concepts have now been joined to help with the treatment of patients with non-Hodgkin’s lymphoma (NHL).

**NHL**

NHL is a cancer of B-lymphocytes. There are currently about 300,000 cases of NHL in the United States, with >56,000 new cases expected to be diagnosed in 2001. It is the sixth leading cause of cancer death in the United States (3). There are 3 histologic grades of NHL: low-, medium-, and high-grade disease. These 3 types differ with respect to their speed of progression, their patterns of response to chemotherapy, their patterns of relapse after chemotherapy, and the average patient life expectancy. Patients who have received treatment for low-grade disease may relapse with progression to intermediate- or high-grade disease or transformed low-grade disease (4,5). There are currently about 140,000 patients with low-grade or transformed low-grade disease, representing almost half of all NHL patients. The lack of curative treatments for patients with advanced low-grade disease has prompted the search for new treatment methods (6).

**THERAPEUTIC USE OF ANTIBODIES**

Immunotherapy uses a monoclonal antibody designed to recognize and bind to a specific protein found on tumor cells. Bound antibody can inhibit tumor cells directly, causing apoptosis, so-called programmed cell death. This phenomenon is a genetically mediated central part of normal development and plays an essential role in organogenesis, tissue homeostasis, and removal of autoreactive clones by the immune system. It affects scattered individual cells and is not associated with an inflammatory response, as opposed to the more familiar necrosis, which usually involves groups of contiguous cells in an inflammatory response to injury or a toxin. Antibody bound to tumor cells can also trigger the immune system to attack these cells, including activation of circulating complement and mobilization of killer lymphocytes (7,8).

Radioimmunotherapy is a 2-pronged approach to cancer treatment that combines an attached $^{92}$I-emitting radionuclide with a monoclonal antibody. This combined agent retains the immunologic effects associated with antibody binding to cells with preferential targeting of radiation to the tumor cells, thereby minimizing the radiation to normal tissues. An additional advantage of this technique is the ability of the agent to kill tumor cells that are not directly visible to the antibody. Such shielded cells may still be hit by the $\beta$-particles emitted by the radionuclide bound to adjoining cells, a process sometimes referred to as the crossfire effect. The mean pathlength of the $\beta$-particle emitted by $^{131}$I is 0.8 mm (about 70–80 times the diameter of a lymphocyte), enough to irradiate tumor masses while minimizing the radiation absorbed dose to adjacent normal tissues. Side effects associated with radioimmunotherapy are primarily hematopoietic.
logic, such as a reversible decrease in blood counts. Some patients may also experience mild flu-like symptoms.

To target the tumor cells as precisely as possible, it is desirable to create an antibody to a stable, tumor-specific, cell-surface antigen. In the case of hematologic malignancies, it is highly desirable to minimize damage to stem cells in the bone marrow. These cells should be spared to allow the patient to repopulate the blood with the normal cellular complement once the therapy dose has done its job. In the case of B-cell lymphomas, such as NHL, one suitable antigen is the CD20 antigen. This is a transmembrane phosphoprotein that is expressed on pre-B-cells and mature B-lymphocytes but not on undifferentiated pluripotent stem cells, the more differentiated lymphoid stem cells, plasma cells, or nonhematologic normal tissues (Fig. 1).

**TOSITUMOMAB PROTOCOL**

Tositumomab (Bexxar; Corixa Corp., South San Francisco, CA) is an anti-B1 murine monoclonal antibody that binds to the CD20 antigen. The antigen is neither shed nor internalized after antibody binding, ensuring that a good immune response can be generated. It is possible to label tositumomab with $^{131}$I without losing its immunologic specificity. Radioimmunotherapy with tositumomab consists of the administration of a combination of unlabeled antibody and antibody labeled with $^{131}$I. A saturated solution of potassium iodide is given from the day before the dose through 14 d after the therapy dose. Patients initially receive a 450-mg infusion of unlabeled tositumomab (predose) over the course of 1 h, followed by a 20-min infusion of 35 mg $^{131}$I-tositumomab and a 10-min saline flush. The predose, in addition to exerting the immune-related cytotoxic response, is thought to bind to nontumor B-cells in the circulation and in the liver and spleen. Animal studies have shown that tumor uptake of radiolabeled antibody is higher after a predose than without a predose, whereas uptake in normal tissue is unchanged. This effect may be due to slower clearance of the radiolabeled antibody from the circulation and enhanced penetration of radiolabeled antibody into the tumor. The change in biodistribution in a patient is illustrated in Figure 2.

**THERAPEUTIC DOSE DETERMINATION**

Different patients will have differing biologic clearances of the radiolabeled antibody, which will change the total radiation absorbed dose to the patient and to the tumor for a given amount of administered activity. To deliver the maximum suggested total body dose of 75 cGy, patients with fast biologic clearances would require a high administered dose and those with slow clearance would require a low administered dose (Fig. 3). The tositumomab treatment regimen starts by administering a small initial dosimetric dose to measure each patient’s individual biologic clearance. This information allows the therapeutic dose to be tailored to the clearance rate so that the desired radiation absorbed dose will be delivered. This approach is conceptually similar to a long-standing nuclear medicine practice of adjusting therapeutic $^{131}$I doses for hyperthyroidism on the basis of the patient’s 24-h radioiodine uptake.

The initial dosimetric data are collected after administration of the same quantity of unlabeled and radiolabeled antibody as will be used for the therapeutic dose, but with only 185 MBq (5 mCi) $^{131}$I attached to the radiolabeled tositumomab. Measurements are made at 3 time points: immediately after injection; on the second, third, or fourth day; and on the sixth or seventh day. Three sets of data are collected: patient counts, counts from an $^{131}$I standard, and background counts. All counts are made from computer-acquired, whole-body camera images. Each scan may be performed rapidly, with scan times of $\leq 2$ min being sufficient. The scans of the standard capsule serve as a quality control step to ensure that there are no variations in counts due to technical problems. The background-corrected patient counts are used to determine the dose residence time,

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**FIGURE 1.** Graphic representation of developmental stages of B-lymphocytes from undifferentiated stem cells to plasma cells. Predominant location of these cell types, degree of expression of CD20 antigen, and associated malignant transformations are shown. CML = chronic myelogenous leukemia; CLL = chronic lymphocytic leukemia.
which is the time required for the activity to fall to $1/e$ (about 37%) of its initial value. The dose residence time in turn can be used to calculate the size of the therapeutic dose that is necessary to give the desired total-body exposure. On the basis of the initial dosimetric calculations, most patients receive a therapeutic dose of 2,590–3,330 MBq (70–90 mCi) $^{131}$I-tositumomab, but there is a wide variation in the dose range (Fig. 4).

**TOSITUMOMAB ADMINISTRATION**

Infusion of the tositumomab requires some preparation but is not difficult. The initial unlabeled antibody dose may be administered in the hematology department, which is set up to deliver and monitor therapeutic infusions. The 450-mg tositumomab dose is administered in a 50-mL volume of saline over the course of 1 h. An indwelling catheter should be used for the infusion to avoid extravasation. Butterflies should not be used. The patient should be premedicated with oral acetaminophen and antihistamine, unless they are contraindicated. The infusion is given through a 0.22-μm filter. The infusion rate should be slowed or the infusion should be temporarily stopped if the patient develops fever, rigors, mucosal edema, or hypotension. Serious reactions such as anaphylaxis are unlikely, but support equipment should be available.

The $^{131}$I-tositumomab (35 mg) infusion is given shortly after the unlabeled antibody infusion. This dose must be administered in a controlled radiation area, usually the nuclear medicine department. The dose is given in a volume of 30 mL over 20 min and is followed by a 30-mL saline flush over 10 min. The venous catheter that was used for the unlabeled antibody infusion may be used for this infusion. A 0.22-μm filter is again used, placed adjacent to the syringe or vial containing the dose. The floor, infusion setup, and any other area that might become contaminated should be draped. All connections should be double-checked to make sure that they are secure and should be visible during the infusion process so that any leaks can be detected. The venous catheter site should also be monitored for extravasation.

Therapeutic doses of tositumomab are typically around 3,330 MBq (90 mCi) $^{131}$I and may be as high as 5,550 MBq (150 mCi). It is possible that the entire dose could fail to reach the patient and spill, as happened with our laboratory’s first administration of the therapy dose. This should not be a cause for panic. Rather, the standard radiation safety procedures should be followed. The spill should be contained and the area should be closed off. Absorbent material should be used to take up the radioactive solution. The patient and personnel should be decontaminated if necessary. The radiation safety officer should be notified as

**FIGURE 2.** Anterior whole-body images from same patient taken 1 h after injection of $^{131}$I-tositumomab. (Left) Image shows biodistribution without predose of unlabeled tositumomab, with most activity in spleen. (Right) Image, for which patient had received unlabeled predose, shows markedly less splenic uptake and better visualization of rest of body.

**FIGURE 3.** Total radiation dose from $^{131}$I-tositumomab is dependent on rate of biologic clearance of radiopharmaceutical. Patients with rapid clearance require higher treatment dose than those with slow clearance to deliver same absorbed dose. Total administered dose is proportional to area under curve.
soon as possible. At worst, residual activity on the floor will need to be covered with lead until it decays. Because the $^{131}$I is bound to the antibody, volatilization of the $^{131}$I is not an immediate problem.

A sample image set and dose calculation are shown in Figure 5 and in Table 1. The 3 data acquisitions for day 0 are shown, along with the patient images from days 4 and 6. Note that the image immediately after infusion shows a prominent cardiac blood pool, which is not seen on later images that have more uptake in the spleen. The image quality is not good because of the short acquisition time, but the goal here is to determine the amount of activity, not to provide morphologic information. The $^{131}$I source measurements in the dose calibrator and from the gamma-camera images serve as a quality control mechanism. The background-corrected counts per megabecquerel (millicurie) should be constant. Too great a deviation from a constant value indicates an error in technique. The background-corrected patient counts are used to model an exponential clearance rate for the radiolabeled tositumomab. In our experience, using the first 2 time points alone gives an excellent estimate of the residence time. The residence time and a parameter called “activity hours” are used to calculate the amount of $^{131}$I activity necessary to administer the required radiation absorbed dose. The activity hours parameter is obtained from a table (generated by the manufacturer from pooled pharmacokinetic data and MIRD dosimetry calculations) and is based on the patient’s height and weight.

**PATIENT RELEASE CRITERIA**

The high doses of $^{131}$I that are administered raise the issue of whether a treated patient can go home after receiving the therapeutic dose. For many years the Nuclear Regulatory Commission (NRC) specified that a patient must have a body burden of $<1,110$ MBq ($<30$ mCi) $^{131}$I or that the measured dose rate at 1 m be $<0.05$ mGy/h ($<5$ mrad/h) for the patient to be released from the hospital. In 1997 the NRC promulgated a new rule, 10 CFR 35.75 (presented in a revision of Title 10, Part 35.75, of The Code of Federal Regulations) (9), which made some adjustment in the above criteria but also allowed the use of patient-specific calculations, the methodology for which was described in Regulatory Guide 8.39: Release of Patients Administered Radioactive Materials (10). These calculations are based on the principle that individuals exposed to the patient receive no more than 5 mSv (500 mrem). In comparison, the annual

![FIGURE 4. Distribution of administered doses of $^{131}$I-tositumomab required to deliver total administered dose of 75 cGy in group of 201 patients enrolled in clinical trials.](image)

![FIGURE 5. Images (scan speed, 100 cm/min) obtained as part of dosimetric study of patient enrolled in clinical trial. Background and standard images are similar at all time points; changes in distribution and clearance of activity are seen on patient images taken at 3 time points.](image)
natural background radiation exposure is about 3 mSv (300 mrem). To comply with these regulations, several requirements must be fulfilled. The institution must maintain records of the basis for releasing the patient. These must include an interview with the patient to determine potential exposure to others, dose rate measurements if dose rate criteria are used, and a copy of the written instructions that must be given to the patient. If the facility is in an agreement state, it is necessary to determine if methods described in Regulatory Guide 8.39 can be used without special permission, if special written permission is required, or if the state uses the more restrictive older guidelines.

If Regulatory Guide 8.39 (10) criteria are used, factors to be considered include the ability of the patient to follow instructions, the ability of the patient to care for him- or herself, the ability of the patient to avoid others (e.g., stay home from work), exposure to others during the patient’s trip home, and whether the patient has urinary incontinence. It is also necessary to determine the occupancy factor for the individuals with the greatest contact with the patient. The occupancy factor is the fraction of the day that is spent within 1 m of the patient. This factor is commonly assumed to be 0.25 unless there is specific reason to change it. Also required are the patient’s residence time, as a measure of how fast the radioactivity is leaving the patient’s body, and the measured dose rate at 1 m from the patient. To complete the calculations, 1 of 2 additional items is needed. The first is based on the administered activity and consists of tables giving the releasable dose rate based on the administered dose, the residence time, and the occupancy factor. The second calculates the exposure to those individuals around the patient, using a formula derived by the manufacturer:

\[
\text{Total exposure (mSv [mrem])} = \frac{\text{occupancy factor} \times \text{dose rate (mSv/h [mrem/h])} \times (7.15 + 0.99 \times \text{residence time [h]})}{75.4 \text{ (day 0)} \quad 76.9 \text{ (day 6)}}
\]

This exposure must be <5 mSv (<500 mrem). Instructions to the patients must include information about sources of potential contamination (i.e., the routes of excretion) and duration of precautions to be observed, including maintaining distance (1.83 m) from others, maintaining separate sleeping arrangements, precautions in common-use bathrooms, segregation and separate washing of utensils and laundry (hold laundry 1 wk before washing), minimizing time in public places, staying home from work, and avoiding contact with pregnant women and children. The durations can be calculated from predetermined factors and the patient’s residence time. An example of such calculation is shown in Table 2. A recently published article (11) assessed

### TABLE 1
Sample Data and Calculations from Patient Dosimetric Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 0</th>
<th>Day 4</th>
<th>Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose calibrator measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of measurement</td>
<td>13:20</td>
<td>12:51</td>
<td>11:30</td>
</tr>
<tr>
<td>[^{131}I] standard activity (kBq [µCi])</td>
<td>9,694 (262)</td>
<td>6,993 (189)</td>
<td>5,846 (158)</td>
</tr>
<tr>
<td>Gamma-camera counts (whole-body mode)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[^{131}I] source</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time started</td>
<td>13:11</td>
<td>12:52</td>
<td>11:19</td>
</tr>
<tr>
<td>Anterior counts</td>
<td>35,925</td>
<td>24,309</td>
<td>20,411</td>
</tr>
<tr>
<td>Background</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time started</td>
<td>13:05</td>
<td>12:42</td>
<td>11:14</td>
</tr>
<tr>
<td>Anterior counts</td>
<td>2,544</td>
<td>2,510</td>
<td>2,345</td>
</tr>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time started</td>
<td>14:13</td>
<td>13:01</td>
<td>11:27</td>
</tr>
<tr>
<td>Anterior counts</td>
<td>327,581</td>
<td>125,248</td>
<td>74,381</td>
</tr>
<tr>
<td>Quality control calculation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from initial count (h)</td>
<td>0</td>
<td>95.7</td>
<td>142.1</td>
</tr>
<tr>
<td>Background-corrected source counts</td>
<td>33,381</td>
<td>21,799</td>
<td>18,066</td>
</tr>
<tr>
<td>% initial count</td>
<td>100</td>
<td>65</td>
<td>54</td>
</tr>
<tr>
<td>Counts per 37 kBq (µCi) in standard</td>
<td>127.4</td>
<td>115.3</td>
<td>114.3</td>
</tr>
<tr>
<td>Residence time calculation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background-corrected patient counts</td>
<td>325,037</td>
<td>122,738</td>
<td>72,036</td>
</tr>
<tr>
<td>% initial count</td>
<td>100</td>
<td>38</td>
<td>22</td>
</tr>
<tr>
<td>Residence time (h) from graph</td>
<td>98</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Therapy dose calculation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administered [^{131}I] dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(activity hours \times desired total-body dose)</td>
<td>75.4</td>
<td>76.9</td>
<td></td>
</tr>
</tbody>
</table>

\[\text{(residence time \times 75 cGy)}\]

Whole-body scan speed, 100 cm/min; collimator, medium energy; patient platelet count, 133,000; patient height, 165 cm; maximum effective mass (from table), 78.7 kg; camera height above table, 36 cm; whole-body scan field of view, 179 cm; desired total-body dose, 65 cGy; patient weight, 82.5 kg; activity hours (from table), 8,523.
the efficacy of these release criteria by comparing radiation absorbed doses measured by dosimeters worn by family members with the predicted radiation absorbed doses. These investigators found that all radiation absorbed doses were <5 mSv (<500 mrem) and that the average radiation absorbed dose was 32% of that predicted, with a range of 4%–98% of that predicted.

INITIAL CLINICAL RESULTS

It is not the purpose of this article to review in detail the clinical results of the various trials that have been conducted. However, the results are quite encouraging. In 5 trials designed for nonmyeloablative therapy in clinically different groups of patients involving a total of 320 patients, >40% demonstrated a complete response, with partial responses seen in an additional 33%. Response rates are good even in patients refractory to standard therapies, and duration of response is relatively long (many months to years). Radioimmunotherapy causes a decrease in red blood cell, white blood cell, and platelet counts, which reach their nadirs 4–7 wk after therapeutic dose administration. Few patients experience such sharp declines as to be at serious risk for complications. Nonhematologic complications are generally mild or moderate and are almost never a serious clinical problem (12–16).

CONCLUSION

At the time of writing of this article clinical data have been submitted to the Food and Drug Administration seeking approval for routine clinical use. Although this form of therapy is different from what we have done in nuclear medicine in the past, almost all clinical laboratories should be able to follow the procedures outlined here to provide an important mode of therapy and new hope for patients with NHL.

**REFERENCES**


**TABLE 2**

Calculations for Determining Release Criteria and Length of Time for Observing Precautions After Therapy

<table>
<thead>
<tr>
<th>Measured residence time</th>
<th>96 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured dose rate at 1 m after therapy</td>
<td>0.1 mSv/h (10 mrem/h)</td>
</tr>
<tr>
<td>Releasable dose rate (from table)</td>
<td>0.2 mSv/h (20 mrem/h)</td>
</tr>
<tr>
<td>Calculated exposure to others (0.25 × 0.1 × [7.15 + 0.99 × 96])</td>
<td>2.56 mSv (255.5 mrem)</td>
</tr>
<tr>
<td>Duration of precautions from table provided by manufacturer</td>
<td></td>
</tr>
<tr>
<td>Sleep at least 1.83 m from others (0.098 × 96)</td>
<td>9.4 d</td>
</tr>
<tr>
<td>Do not take long trip (&gt;4 h) near others (0.019 × 96)</td>
<td>1.8 d</td>
</tr>
<tr>
<td>Stay at least 1.83 m from pregnant women and children (&lt;1 mSv [&lt;100 mrem] exposure) (0.135 × 96)</td>
<td>13 d</td>
</tr>
</tbody>
</table>

**REFERENCES**

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