Yttrium 90 ibritumomab tiuxetan consists of the murine monoclonal antibody ibritumomab securely bound to the second-generation chelator tiuxetan, which attaches the high-energy pure β emitter 90Y, for therapy, or the γ emitter indium 111, for imaging. The biodistribution of the therapeutic dose of 90Y ibritumomab tiuxetan can be predicted by using an imaging dose of the antibody labeled with 111In. Calculation of the therapeutic dose is simple and is based on patient weight and baseline platelet count: for patients with a platelet count of less than 100 × 10^9/L to 149 × 10^9/L the dose is reduced to 0.3 mCi/kg; and the total dose should not exceed 32 mCi. Patients with platelet counts of less than 100 × 10^9/L should not be treated with 90Y ibritumomab tiuxetan. Imaging with 111In ibritumomab tiuxetan is performed only to assess biodistribution of the radioimmunoconjugate. Uptake in sites of pathologic adenopathy, as well as other areas of lymphomatous involvement, is frequently seen on the images, but visualization of tumor uptake is not required to proceed with the therapeutic dose of 90Y ibritumomab tiuxetan.

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Imaging and Dosing in Radioimmunotherapy With Yttrium 90 Ibritumomab Tiuxetan (Zevalin)

Stewart M. Spies

THE POTENTIAL advantages of using radio-labeled immunologically active molecules for the detection and treatment of malignant disorders have been appreciated for decades. Early studies using polyclonal antibodies and more recent trials using monoclonal antibodies have shown the feasibility of using tumor-specific or tumor-predominant antigens as targets for diagnostic and therapeutic radioimmunoconjugates. Several agents, including 99mTc arcitumomab (CEA-Scan; Immunomedics, Inc, Morris Plains, NJ), 111In satumomab pendetide (OncoScint; Cytogen Corp, Princeton, NJ), and 111In capromab pendetide (ProstaScint Cytogen Corp) have been approved by the US Food and Drug Administration for diagnostic use and have enjoyed some clinical success. The relatively low count rates and consequently high image noise content with these agents, however, can be limiting factors in image interpretation.

The cornerstone of the technique of radioimmunotherapy (RIT) is the ability to deliver cytotoxic doses of radiation to cells based on antigenic properties that are unique to or at least predominant in malignant tissue, while minimizing the dose to normal tissue. Several factors can impact the efficacy of an RIT agent, including the presence of nonspecific uptake, uptake by normal tissues (including cells in the circulating blood), varying degrees of antigen expression by tumors, and incomplete accessibility of tumor antigen sites to circulating radiopharmaceuticals because of variability in tumor vascularity. Additionally, the selection of the target antigen can also affect the likelihood of successful treatment with RIT. For example, antigens that internalize within tumor cells are less desirable targets because of potential degradation of the labeled antibody once within the cytoplasm, reducing the radiation dose to tumor. Yttrium 90 ibritumomab tiuxetan targets the CD20 antigen, which is present on more than 90% of B-cell lymphomas and is neither shed nor internalized. The ibritumomab tiuxetan regimen uses infusions of the unlabeled chimeric anti-CD20 antibody rituximab before administration of the radioactive compound to decrease circulating B cells and improve tumor targeting.

Most trials of therapeutic radiolabeled monoclonal antibodies to date have used antibodies labeled with either 131I or 90Y. Both of these radionuclides can produce significant radiation doses as they undergo β decay. The path lengths of the β particles from both radionuclides are significantly greater than the diameter of a cell (Eav for 131I = 192 keV, Eav for 90Y = 934 keV), allowing for a “crossfire” effect (Fig 1), in which radiation damage can be achieved in cells remote from the site of antibody binding. As a result, therapeutic radiation doses can be delivered to cells in tumors that are bulky, poorly vascularized, or have heterogeneous antigen expression. In the case of the more energetic 90Y, a β particle could deposit energy at a cell up to 5 mm from the site of decay.

The emission of γ radiation, as with 131I, can be
both an advantage and a liability. The ability to use gamma camera imaging to assess antibody biodistribution and perform patient-specific dosimetry using a relatively low-activity tracer dose, as well as the ability to confirm the distribution of the therapeutic dose, may be advantageous. On the other hand, the penetrating γ radiation of 131I impacts the radiation safety requirements of RIT, often necessitating patient hospitalization or significant restriction of patient activity in an outpatient setting. The absence of emissions in the decay scheme of 90Y removes many radiation safety concerns, as patients undergoing RIT with this radionuclide can be treated as outpatients and released after the radiolabeled antibody injection with only minimal restrictions and precautions. However, the inability to perform useful imaging with 90Y antibodies does require the use of a surrogate radionuclide for evaluation of antibody biodistribution before commencing with RIT. In the case of 90Y ibritumomab tiuxetan, this surrogate is ibritumomab labeled with 111In using the same linker-chelator (tiuxetan) used to conjugate the antibody with yttrium for the therapeutic dose.6,10,11

The moderately high γ energies of 111In (171 and 245 keV) can produce clinically adequate images for assessing biodistribution.1,2,10,12 While 111In imaging typically uses lower administered doses and consequently yields poorer image statistics and longer imaging times than conventional radiopharmaceuticals labeled with technetium 99m, the lower photon energy of 111In as compared with 131I does permit the use of medium-energy collimation for better image quality.

Gamma camera imaging of 111In ibritumomab tiuxetan is performed to confirm the expected biodistribution of the radioimmunoconjugate before administration of the therapeutic dose.4,12 Imaging with 111In ibritumomab tiuxetan is not performed to assess tumor uptake. The safe therapeutic dose of 90Y ibritumomab tiuxetan is calculated by patient weight and baseline platelet count.2,13

**BIODISTRIBUTION**

The US Food and Drug Administration requires an assessment of the biodistribution of an imaging dose of 111In ibritumomab tiuxetan before the administration of the therapeutic dose of 90Y ibritumomab tiuxetan in eligible patients.

Biodistribution is evaluated by using a series of whole-body images that are obtained after the administration of 111In ibritumomab tiuxetan. To deplete circulating B lymphocytes, patients first receive an infusion of rituximab (Rituxan; Genentech, Inc, South San Francisco, CA, and Biogen Idec Inc, Cambridge, MA) 250 mg/m², a chimeric monoclonal antibody which targets the CD20 antigen. The cold antibody infusion decreases circulating B-cell numbers and improves tumor targeting. Within 4 hours after the rituximab infusion, 5 mCi of 111In ibritumomab tiuxetan is administered by slow intravenous push over 10 minutes.

Anterior and posterior images are obtained at 2 to 24 hours after the 111In ibritumomab tiuxetan (scan speed, 10 cm/min) and again at 48 to 72 hours (scan speed, 7 cm/min). An optional set of images may be obtained at 90 to 120 hours (scan speed, 5 cm/min) to resolve discrepancies.

Early images typically show prominent activity in the blood pool, and significant uptake in the liver and spleen, with low activity in the lungs, kidneys, bowel, and urinary bladder. On later images, there is clearance of the blood pool activity with persistence of labeled antibody in the liver and spleen (Table 1).14 Uptake in sites of pathologic adenopathy as well as other areas of lymphomatous involvement is frequently seen on the later images, but visualization of tumor uptake is not required to proceed with the therapeutic dose of 90Y ibritumomab tiuxetan. The approved use of 90Y ibritumomab tiuxetan requires only visual inspection of the images to confirm expected biodistribution (Fig

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**Fig 1. Geometry of unlabeled (naked) antibody (left) and radiolabeled antibody (right), demonstrating the ability to produce cell damage in cells remote from the site of antibody binding (crossfire effect).**
No image quantification step is needed to safely proceed with yttrium therapy. Altered biodistribution is rare, with an incidence of less than 1% since US Food and Drug Administration approval of the compound. Among the patterns of altered biodistribution which have been noted are: renal uptake greater than liver on the 48–72 hour images; pulmonary uptake greater than liver on the 48–72 hour images (in the absence of pulmonary involvement with lymphoma); prominent bowel uptake greater in magnitude to liver uptake on 48–72 hour images; accelerated clearance of activity from the blood, with poor visualization of blood pool on the initial (2–24 hour) images (Table 2). Altered biodistribution is a contraindication to proceeding with the therapeutic dose. If expected biodistribution is seen, patients can proceed to the therapeutic dose of $^{90}$Y ibritumomab tiuxetan.

**DOSING AND SAFETY**

Once expected biodistribution of $^{111}$In ibritumomab tiuxetan has been confirmed, the patient’s weight and pretreatment platelet count are used to determine the dose of $^{90}$Y ibritumomab tiuxetan. In patients with a platelet count of $150 \times 10^9/L$ or greater the dose of $^{90}$Y ibritumomab tiuxetan is 0.4 mCi/kg. In patients with mild thrombocytopenia (platelet count $100 \times 10^9/L$ to $149 \times 10^9/L$) the dose is reduced to 0.3 mCi/kg. Patients with platelet counts of less than $100 \times 10^9/L$ should not be treated with $^{90}$Y ibritumomab tiuxetan, and in no case should the total dose of $^{90}$Y ibritumomab tiuxetan exceed 32 mCi.

The therapeutic dose of $^{90}$Y ibritumomab tiuxetan is given 7 to 9 days after the imaging dose, and, as with the imaging dose, it is preceded by an infusion of rituximab 250 mg/m$^2$. The therapeutic dose is also given by slow intravenous push over 10 minutes within 4 hours after the rituximab infusion. It is important to closely monitor the injection to ensure that the entire dose is delivered intravenously.

Several clinical trials have shown the safety of this therapy. The doses to uninvolved organs are expected to be less than 2,000 cGy, and to the red marrow less than 300 cGy. When used in accordance with the patient selection criteria in the package insert, toxicity to major organs is not expected, and the principal expected toxic effect is delayed, transient hematologic toxicity.

The safety and efficacy of therapy using $^{90}$Y

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**Table 1. Expected Biodistribution**

<table>
<thead>
<tr>
<th>Blood pool</th>
<th>Scan 2–24 h</th>
<th>Scan 48–72 h</th>
<th>Scan 90–120 h (Optional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver and spleen</td>
<td>Present</td>
<td>Decreases</td>
<td>Decreases</td>
</tr>
<tr>
<td>Kidneys, urinary bladder, bowel</td>
<td>Moderately high to high</td>
<td>Moderately high to high</td>
<td>Moderately high to high</td>
</tr>
<tr>
<td>Tumor</td>
<td>Variable</td>
<td>Decreases</td>
<td>Decreases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderately low to very low</td>
<td>Moderately low to very low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variable</td>
<td>Variable</td>
</tr>
</tbody>
</table>
ibritumomab tiuxetan, a murine monoclonal antibody targeted to the CD20 cell surface antigen, has been shown in clinical trials involving over 700 patients with non-Hodgkin’s lymphoma. The biodistribution of the therapeutic dose can be predicted using $^{111}$In-labeled ibritumomab tiuxetan, and whole body clearance calculations are not necessary for the safe use of this agent. Using a simple dosing strategy based on patient weight (and modified for patients with mild thrombocytopenia), therapeutic radiation doses in areas of lymphomatous involvement can be achieved, while normal organ doses are acceptable and have not resulted in incidences of significant organ dysfunction. Hematologic toxicity is commonly observed, but is generally transient and reversible.

REFERENCES