Logistics of Radioimmunotherapy With Yttrium 90 Ibritumomab Tiuxetan (Zevalin)

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Radioimmunotherapy is a promising new therapeutic option for the treatment of B-cell non-Hodgkin’s lymphoma. Several monoclonal antibody and radionuclide conjugates, including I-131 tositumomab and Y-90 ibritumomab, have been investigated in clinical trials. Yttrium 90 ibritumomab tiuxetan (Zevalin; Biogen Idec Inc, Cambridge, MA) is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin’s lymphoma, including patients with rituximab-refractory follicular non-Hodgkin’s lymphoma. The ibritumomab tiuxetan regimen requires coordination of a multidisciplinary team on which the nuclear medicine physician (or radiation oncologist) plays a major role. The nuclear medicine physician (or radiation oncologist) is responsible for overseeing the administration of the radioimmunoconjugates and for interpreting the imaging scans to determine the expected or altered biodistribution of the radioimmunoconjugate.

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DOSING SCHEDULE OF 90Y IBRITUMOMAB TIUXETAN

Ibritumomab Tiuxetan Regimen

The dosing schedule of ibritumomab tiuxetan (Fig 1) consists of the administration of rituximab (Rituxan; Genentech, Inc, South San Francisco, CA, and Biogen Idec Inc, Cambridge, MA) 250 mg/m² to improve the biodistribution of the radiolabeled monoclonal antibody, followed within 4 hours by 111In-labeled ibritumomab tiuxetan for imaging, or 90Y-labeled ibritumomab tiuxetan for therapy. It has been shown that predosing with an unlabeled monoclonal antibody to CD20 improves the biodistribution of the radiolabeled antibody, from binding 18% of the known disease sites without a predose of unlabeled antibody to binding up to 92% of the known disease sites after the administration of ibritumomab 1 or 2.5 mg/kg.2,3 The therapeutic dose of 90Y ibritumomab tiuxetan 0.4 mCi/kg (0.3 mCi/kg in patients with a platelet count of 100 × 10⁹/L to 149 × 10⁹/L) is administered 7 to 9 days after the imaging dose of 111In ibritumomab tiuxetan. The maximum total dose of 90Y ibritumomab tiuxetan is 32 mCi. Both 111In ibritumomab tiuxetan and 90Y ibritumomab tiuxetan are administered as 10-minute intravenous infusions through a 0.22-μm low-protein-binding filter. Neither should be administered as a rapid intravenous bolus.

The infusions of rituximab are generally administered in a clinic by the oncology staff, and the radioimmunoconjugates are administered in a nuclear medicine department by workers who have been trained and certified in the use and administration of radiolabeled therapeutics.1 Communication and coordination between the workers at both sites are essential to ensure the safe and effective delivery of the ibritumomab tiuxetan regimen. After the first infusion of rituximab (in the medical oncology office) the patient is given the imaging dose of 111In ibritumomab tiuxetan 5 mCi (in the nuclear medicine department) and undergoes two gamma scans. (A third scan is optional and may be performed to rule out any ambiguities.) From these scans the nuclear medicine physician confirms that...
the biodistribution of the radioimmunoconjugate is as expected and continues with the therapeutic regimen. (If the nuclear medicine physician determines that the biodistribution is altered, the patient should not be treated with \textsuperscript{90}Y ibritumomab tiuxetan.) Although no cases of altered biodistribution were observed during the registrational trials, altered biodistributions have been observed in less than 1% of patients treated with ibritumomab tiuxetan.\textsuperscript{4,5} The therapeutic phase occurs 7 to 9 days later, when the patient is given the second infusion of rituximab and within 4 hours the therapeutic dose of \textsuperscript{90}Y ibritumomab tiuxetan.

**Pharmacokinetics of \textsuperscript{90}Y Ibritumomab Tiuxetan**

The pharmacokinetics of \textsuperscript{90}Y ibritumomab tiuxetan have been estimated from measurements of the activity of \textsuperscript{90}Y in the blood or plasma in phase I-II and phase III studies.\textsuperscript{4,5} In a phase I-II study in 57 patients with relapsed or refractory low-grade, intermediate-grade, or mantle cell non-Hodgkin’s lymphoma, the median effective half-life of \textsuperscript{90}Y in the blood and plasma was estimated to be 28 hours (range, 14 to 36 hours). The median biologic half-life of the antibody was 48 hours (range, 18 to 77 hours).\textsuperscript{4} The \textsuperscript{90}Y area under the time-concentration curve was estimated to be 24 and 22 \(\mu\text{g} \cdot \text{h/mL}\) in the blood and the plasma, respectively (range, 4 to 48 \(\mu\text{g} \cdot \text{h/mL}\)). In a phase III study in 143 patients with non-Hodgkin’s lymphoma (73 patients treated with \textsuperscript{90}Y ibritumomab tiuxetan), the median effective half-life of \textsuperscript{90}Y in the blood was 27 hours (range, 17 to 44 hours) and the median biologic half-life of the antibody was 47 hours (range, 22 to 140 hours).\textsuperscript{5}

**Imaging With Ibritumomab Tiuxetan**

Imaging with a fixed dose of \textsuperscript{111}In ibritumomab tiuxetan 5 mCi is performed to confirm the expected biodistribution of the antibody before the therapeutic dose of \textsuperscript{90}Y ibritumomab tiuxetan is given.\textsuperscript{13} Whole body anterior and posterior gamma scan images are obtained at 2 to 24 hours and at 48 to 72 hours after the administration of \textsuperscript{111}In ibritumomab tiuxetan (with an optional third scan at 90 to 120 hours).\textsuperscript{12}

Expected biodistribution of \textsuperscript{111}In ibritumomab tiuxetan is defined as easily detected uptake in the blood pool areas on the first images, with less activity on the second and third images; moderately high or high uptake in the normal liver and spleen on the first, second, and third images; and moderately low or very low uptake in the kidneys, urinary bladder, and bowel on all images (Fig 2).\textsuperscript{2,6} Altered biodistribution of \textsuperscript{111}In ibritumomab tiux-
etan is characterized by diffuse uptake in the normal lung, which is more intense than that in the cardiac blood pool on the first images or more intense than the uptake in the liver on the second or third images; uptake in the kidneys more intense than that in the liver on the posterior view of the second or third images; or more intense areas of uptake throughout the normal bowel compared with the uptake in the liver on the second or third images. Although extremely rare, altered biodistribution is sufficient to halt treatment. Imaging, however, has not been shown to effectively indicate, and should therefore not be interpreted to assess, tumor uptake.

PREPARATION OF IBRITUMOMAB TIXETAN

Ibritumomab tiuxetan is supplied in two separate kits that contain all the nonradioactive components necessary to prepare a single dose of $^{111}$In ibritumomab tiuxetan and $^{90}$Y ibritumomab tiuxetan. These include $^{111}$In chloride sterile solution (for $^{111}$In ibritumomab tiuxetan), $^{90}$Y chloride sterile solution (for $^{90}$Y ibritumomab tiuxetan), and three sterile 1-mL syringes, one sterile 3-mL syringe, two sterile 10-mL syringes with 18- to 20-gauge needles, instant thin-layer chromatography silica gel strips, 0.9% sodium chloride solution for the chromatography solvent, developing chamber for chromatography, suitable radioactivity-counting apparatus, low-protein-binding 0.22-μm filters, and vial and syringe shields (for both $^{111}$In and $^{90}$Y ibritumomab tiuxetan).

Detailed directions for labeling $^{111}$In ibritumomab tiuxetan and $^{90}$Y ibritumomab tiuxetan are provided in the ibritumomab tiuxetan prescribing information, and are briefly described below. The radiolabeling of $^{111}$In ibritumomab tiuxetan and $^{90}$Y ibritumomab tiuxetan is performed at local commercial radiopharmacies, and the $^{111}$In- or $^{90}$Y-labeled ibritumomab tiuxetan is delivered to the clinic for on-site dose preparation and administration.

Labeling of $^{111}$In Ibritumomab Tiuxetan

Before the labeling reaction is initiated, the components of the kit are allowed to reach room temperature and the quantity of each component necessary for the labeling reaction is determined. The $^{111}$In ibritumomab tiuxetan labeling reaction must contain 5.5 mCi of $^{111}$In chloride (available commercially), sodium acetate 50 mmol/L (1.2 times the volume of the 5.5 mCi of $^{111}$In chloride), and 1.0 mL of ibritumomab tiuxetan (1.6 mg/mL). After the addition of each component to the reaction vial (in the order of sodium acetate, $^{111}$In, and ibritumomab tiuxetan) the reaction mixture is mixed by gentle inversion or rolling. The labeling reaction is allowed to proceed at room temperature.
for exactly 30 minutes, followed immediately by
the addition of formulation buffer to bring the final
volume of the preparation to 10 mL. The volume
required for a dose of $^{111}$In ibritumomab tiuxetan 5
mCi is then withdrawn from the reaction vial with
a 10-mL syringe fitted with an 18- to 20-gauge
needle, and the syringe and its contents are assayed
in a dose calibrator. The syringe should contain the
exact dose to be administered to the patient and
should be clearly marked with the patient identi-
fication, the date and time of preparation, the total
activity and volume, and the date and time of
expiration. $^{111}$In ibritumomab tiuxetan is stored at
2 to 8°C until use, and should be administered
within 12 hours after radiolabeling.2

**Labeling of $^{90}$Y Ibritumomab Tiuxetan**

The labeling procedure for $^{90}$Y ibritumomab
tiuxetan is similar to that for $^{111}$In ibritumomab
tiuxetan, but significant differences do exist. The
$^{90}$Y ibritumomab tiuxetan labeling reaction must
contain 40 mCi of $^{90}$Y chloride (shipped direct
from a commercial supplier when the $^{90}$Y ibritu-
momab tiuxetan kit is ordered), sodium acetate 50
mmol/L (1.2 times the volume of the 40 mCi of
$^{90}$Y chloride), and 1.3 mL of ibritumomab tiuxetan
(1.2 mg/mL). After the addition of each component
to the reaction vial (in the order of sodium acetate,
$^{90}$Y, and ibritumomab tiuxetan) the reaction mix-
ture is mixed by gentle inversion or rolling. The
labeling reaction is allowed to proceed at room
temperature for exactly 5 minutes, and formulation
buffer is immediately added to the reaction vial to
bring the final volume of the preparation to 10
mL.2 The volume required for a dose of $^{90}$Y
ibritumomab tiuxetan 0.4 mCi/kg (in patients with
a platelet count $\geq 150 \times 10^9/L$) or 0.3 mCi/kg (in
patients with a platelet count of $100 \times 10^9/L$ to
$149 \times 10^9/L$) is then withdrawn from the reaction
vial with a 10-mL syringe fitted with an 18- to
20-gauge needle, and the syringe and its contents
are assayed in a dose calibrator. After the addition of
the prescribed dose (within 10% of the actual
prescribed dose; maximum of 32 mCi) and
should be clearly marked with the patient identi-
fication, the date and time of preparation, the total
activity and volume, and the date and time of
expiration. $^{90}$Y ibritumomab tiuxetan is stored at 2
to 8°C until use, and should be administered
within 8 hours after radiolabeling.2

**Quality Control of $^{111}$In Ibritumomab
Tiuxetan and $^{90}$Y Ibritumomab Tiuxetan**

The quality control and safety measures for
radiolabeled antibodies for clinical use are stringent. It is necessary to determine the radioactivity in millicuries per milliliter, the identity of the anti-
body and radioisotope, the retention of antibody
activity, physical integrity, absence of pyrogens,
sterility, and radiochemical purity (percentage of
free radionuclide) of the radioimmunoconjugate.7

The radiochemical purity of $^{111}$In ibritumomab
tiuxetan and $^{90}$Y ibritumomab tiuxetan is deter-
mained by instant thin-layer chromatography with
silica gel strips. Indium 111 ibritumomab tiuxetan
and $^{90}$Y ibritumomab tiuxetan can be released if
the radiochemical purity test is at least 95%.1,2

**CALIBRATION OF DOSE CALIBRATOR**

The patient’s doses of $^{111}$In ibritumomab tiux-
etan and $^{90}$Y ibritumomab tiuxetan should be
measured immediately before their administration
by using a suitable calibration system. The dose
calibrator must be operated according to the man-
ufacturer’s instructions for measuring $^{111}$In or $^{90}$Y.
Because dose calibrators are designed to assay
gamma emissions and $^{90}$Y is a pure beta emitter,
accurately assaying $^{90}$Y requires correcting the
calibration setting for $^{90}$Y for different geometries.
Instructions for $^{90}$Y calibration are provided in Fig
3. Additionally, Geiger-Müller survey counters can
be calibrated to accurately detect $^{90}$Y low-energy
bremsstrahlung.13 If the dose of $^{90}$Y ibritumomab
tiuxetan is supplied by the radiopharmacy as a unit
dosage, only a single dose calibrator dial setting is
required for accurate dose calibrator measurement
for all $^{90}$Y ibritumomab tiuxetan activity prescrip-
tions, with no correction required for different
volumes.8

**RADIATION SAFETY ISSUES**

**Shielding Requirements**

Because the ibritumomab tiuxetan regimen uses
$^{111}$In and $^{90}$Y, the radiolabeled compounds must be
safe for patients and personnel involved in label-
ing, handling, and transporting these agents. Radia-
tion exposure to healthcare workers and the pa-
tient’s family members from $^{90}$Y is low.1,9 The use
of vial, syringe, and transport shields is mandatory
to reduce radiation exposure. The use of acrylic
1. Set “background activity” to zero.
2. Set “other button” dial to manufacturer’s suggested setting for 90Y (48) with “manual setting” dial.
3. Draw 40 mCi 90Y with 1-mL TB syringe.
5. Assay 1-mL syringe starting at 048 setting (starting dial setting for Capintec).
6. Change manual dial setting until 4.0 mCi is displayed, multiply by 10.
7. Transfer 40 mCi to glass reaction vial and QS to 10.0 mL total volume.
8. To determine actual activity added to reaction vial, assay residual activity left in 1-mL syringe and subtract from 40 mCi.
9. Using 10-mL syringe, remove and assay consecutive 1-mL aliquots from reaction vial and assay until entire volume of 90Y is in 10-mL syringe.
10. Change manual dial setting at each aliquot to equal calculated activity contained in table shown in 3B.
11. Record dial setting at each volume—aliquot in 3B.

Use dial settings from table to plot graph for slope as shown in 3C.

Fig 3. Calibrating the dose of 90Y ibritumomab tiuxetan. (A) Instructions for 90Y calibration, (B) typical calibration of 10-mL syringe containing 40 mCi of 90Y, (C) typical calibration plot for a syringe containing a 40-mCi source of 90Y.

shields or composite (either acrylic/lead or aluminum/lead) shields is essential to reduce bremsstrahlung production. Use of acrylic or composite vial shields and syringe shields reduced the radiation levels from 3.66 Gy/hour to 1 to 2 mGy/hour (from a 41.9-mCi 90Y ibritumomab tiuxetan preparation), and from 12.87 Gy/hour to 2 to 3 mGy/hour (from a 10-mL syringe containing 31.0 mCi 90Y ibritumomab tiuxetan). Lead shielding alone should not be used to shield 90Y ibritumomab tiuxetan, because of increased production of bremsstrahlung, which are x-rays emitted when beta particles suffer rapid acceleration. Bremsstrahlung production, using lead shielding alone, is approximately 6%, while using either acrylic or aluminum shielding reduces bremsstrahlung production to less than 1%. Once bremsstrahlung is produced, lead shielding is very effective.

Patient Radiation Safety

Yttrium 90 ibritumomab tiuxetan is routinely and safety administered as an outpatient procedure. The specific bremsstrahlung constant (a newly devised constant analogous to the specific gamma constant) for 90Y in soft tissue in a 70-kg patient is $1.41 \times 10^{-4} \text{C/kg-cm}^2/\text{MBq-hour} (5.64 \times 10^{-3} \text{R-cm}^2/\text{mCi-h})$. This means that the administered dose of 90Y ibritumomab tiuxetan would have to exceed several thousand millicuries to exceed Nuclear Regulatory Commission outpatient exposure limits, which is based on a total effective dose equivalent at 1 m of 0.5 cSv. Because the administered dose of 90Y ibritumomab tiuxetan is usually between 21 and 30 mCi, and is never more than 32 mCi, Nuclear Regulatory Commission requirements for outpatient therapy are uniformly met without additional safety measures.

Moreover, the radiation exposure in the first week after treatment to persons who have contact with a patient who has been treated with 90Y ibritumomab tiuxetan is found to be similar to background radiation. Patients treated with 90Y ibritumomab tiuxetan are released immediately after treatment, and only the standard universal precautions to avoid contact with body fluids are required. The release instructions include cleaning up any spilled urine and disposing of any body
fluid–contaminated material (flushing it down the toilet or placing it in a plastic bag in the household trash) for the first 3 days after the treatment. Patients should also wash their hands thoroughly after using the toilet (for 3 days) and use condoms during intercourse for the first week after treatment.¹

The use of the ibritumomab tiuxetan regimen is regulated by strict safety and quality guidelines. Ibritumomab tiuxetan is generally radiolabeled at local commercial radiopharmacies and is delivered to the clinic for on-site dose preparation and administration. Ibritumomab tiuxetan is provided as a single-dose kit, and the radiolabeled product is released for patient administration if its radiochemical purity is at least 95%.

Treatment with ⁹⁰Y ibritumomab tiuxetan requires an understanding of the materials and procedures that are used with radionuclides. These include using appropriate shielding during labeling, transport, handling, and administration, and following the standard universal precautions to avoid contact with body fluids after treatment with the agent. Nuclear medicine physicians play a key role in the administration of the ibritumomab tiuxetan regimen, especially in interpreting the gamma camera images to assess the biodistribution of the radiolabeled antibody.

REFERENCES

2. Zevalin (ibritumomab tiuxetan) prescribing information. San Diego, CA, IDEC Pharmaceuticals Corporation, 2002