^{90}Y-Ibritumomab Tiuxetan in the Treatment of Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma*

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Objective: Non-Hodgkin's lymphoma (NHL) is the most frequently diagnosed malignancy of the immune system, with more than 53,900 new cases diagnosed in 2002. Conventional cancer therapies cure many, but not the majority of, cases of the aggressive forms of NHL, and the more indolent and follicular forms of the disease that affect nearly half of all patients with NHL are considered incurable. In the absence of cure or survival benefits, treatments such as radioimmunotherapy that induce remission and prolong time off therapy are considered valuable. ^{90}Y-Ibritumomab tiuxetan recently became the first radioimmunotherapy agent to be approved for commercial use by the U.S. Food and Drug Administration. After reading this article, the nuclear medicine technologist should be able to understand the incidence and prevalence of NHL, describe the ibritumomab tiuxetan therapy protocol, explain specific infusion techniques for this protocol, list acquisition parameters after injection of ^{111}In-ibritumomab tiuxetan, and describe specific safety techniques to keep risk as low as reasonably achievable while performing the therapy protocol.

Key Words: non-Hodgkin's lymphoma; radioimmunotherapy; ibritumomab tiuxetan; ^{90}Y; Zevalin

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Ibritumomab tiuxetan (Zevalin; IDEC Pharmaceuticals) labeled with ^{90}Y is a radioimmunotherapeutic agent for the treatment of B-cell non-Hodgkin's lymphoma (NHL). Ibritumomab tiuxetan is composed of a radionuclide conjugated to the antibody ibritumomab, the parent murine antibody of the genetically engineered chimeric murine–human monoclonal antibody rituximab (*1*). Ibritumomab is an IgG1 kappa-monoclonal antibody that, like rituximab, binds specifically to the cluster designation 20 (CD20) antigen that is expressed (located) on pre-B lymphocytes and mature B lymphocytes and on more than 90% of B-cell NHL tumors (*2*). Radioactive metal ions such as ^{90}Y or ^{111}In can be attached to an antibody such as ibritumomab through a metal chelating agent. For this monoclonal antibody, a modified metal chelator, called tiuxetan, was developed. Tiuxetan is linked to ibritumomab by a stable thiourea covalent bond and provides a strong binding site for ^{90}Y or ^{111}In (Fig. 1).

The radioactive metal ^{90}Y is a high-energy pure β-emitter. It delivers a maximum particle energy of 2.3 MeV and has a half-life of 64.1 h, decaying to ^{90}Zr. It has an effective pathlength of 5.3 mm in tissue (*3*), equating to 100–200 cell diameters. When ^{90}Y-ibritumomab tiuxetan binds to CD20 on tumors, it creates a crossfire effect by delivering radiation to the cells it binds to as well as to nearby tumor cells and tumor cells that do not express the antigen or that compose poorly vascularized, bulky tumors (Fig. 2) (*4–6*).

RATIONALE FOR IBRITUMOMAB TIUXETAN

The most common forms of NHL are diffuse large B-cell NHL (31%) and follicular NHL (22%) (*7*). Diffuse large B-cell NHL is considered curable with chemotherapy (*7*), but follicular NHL, which falls into the category of low-grade, or indolent, lymphomas, is often in advanced stages at diagnosis and is usually considered incurable. The indolent lymphomas often follow a pattern of disease remission and then recurrence, with each remission being shorter than the previous one. The median survival in 1,021 patients with indolent lymphoma treated at Stanford University between 1960 and 1992 was 8–10 y (*8*). Indolent lymphomas often undergo histologic transformation to intermediate- or high-grade lymphomas, resulting in median survival of only 17–22 mo, despite aggressive chemotherapy (*9*).

Low-grade follicular or transformed B-cell NHL was diagnosed in more than 53,900 patients in the United States in 2002 (*10*). In contrast to the declining mortality rates for most other cancer types, the mortality rate for NHL is increasing (*11*). Unfortunately, the course of disease progression and survival with indolent lymphomas has not been

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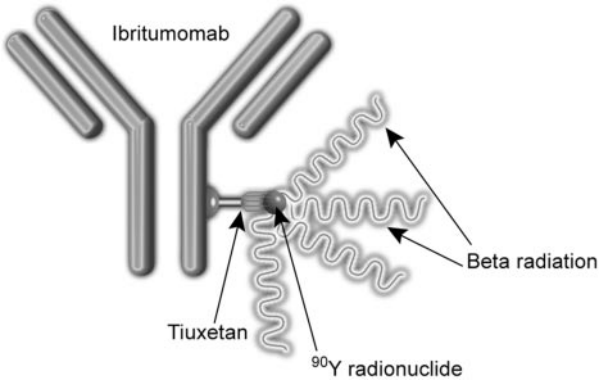

FIGURE 1. Components of ^{90}Y-ibritumomab tiuxetan.

significantly altered by single or multiagent chemotherapy regimens in the last 30 y and continues to present a challenge to oncologists (*9*). The current treatment options include radiation therapy for localized disease, chemotherapy, monoclonal antibodies to CD20 such as rituximab, and bone marrow transplantation. Additional treatment options are needed to increase survival in patients with NHL that has relapsed or has been refractory (resistant) to treatment.

USE OF IBRITUMOMAB TIUXETAN

^{90}Y-Ibritumomab tiuxetan is indicated for the treatment of relapsed or refractory low-grade, follicular, or transformed B-cell NHL and rituximab-refractory B-cell NHL (*12*).

The safety and efficacy of the ibritumomab tiuxetan regimen has been evaluated in 3 multicenter clinical trials. The first was a single-arm study of 54 patients with rituximab-refractory NHL (*13*). The overall response rate (ORR) was 74%, with complete responses in 15% of patients. The median duration of response was 6.4 mo (range, 0.5–24.9+ mo), and the median time to disease progression was 6.8 mo (range, 1.1–25.9+ mo). The second trial randomized patients with relapsed or refractory low-grade or follicular B-cell NHL to ibritumomab tiuxetan ($n = 73$) or rituximab ($n = 70$) (*14*). In the ibritumomab tiuxetan arm of the study, the ORR of 80% was significantly higher than that in the rituximab arm ($P = 0.002$), with complete responses in 30% of patients. The median duration of response was 13.9 mo (range, 1.0–30.1+ mo), and the median time to disease progression was 11.2 mo (range, 0.8–31.5+ mo). In the rituximab arm of the study, ORR was 56%, with complete responses in 16% of patients. The median duration of response was 11.8 mo (range, 1.2–24.5 mo), and the median time to disease progression was 10.1 mo (range, 0.7–26.1 mo). The duration of response and time to disease progression did not differ significantly between the 2 study groups ($P = 0.04$).

The third study was conducted on 30 patients with mild thrombocytopenia (platelet count, 100,000–149,000 cells/mm^3) (*15*). Patients were given a reduced dose of ibritumomab tiuxetan, 11.1 MBq/kg (0.3 mCi/kg). The ORR in an intent-to-treat analysis was 83%, based on International Workshop criteria (*16*); the median time to progression was 9.4 mo, and the median duration of response was 11.7 mo. The hematologic toxicity was more severe in these patients than in those of the other 2 studies but still compared favorably with the adverse effects of chemotherapy regimens; the incidence of grade 4 neutropenia was 33%, and the incidence of grade 4 thrombocytopenia was 13% (*15*).

The response rates with ibritumomab tiuxetan are comparable to those with conventional chemotherapy, which is typically given in a course that can last from 4 to 6 mo. In previously untreated patients with NHL, combination chemotherapy with regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone typically produce ORRs of approximately 70%–95%, depending on the patient population (*17–19*). The ORRs with ibritumomab tiuxetan in the 3 clinical trials cited above ranged from 74% to 83% in relatively heavily pretreated patients who were not expected to respond well to chemotherapy.

Patient selection is important to the success and safety of treatment with the ibritumomab tiuxetan regimen. To prevent myeloablation, it is important that less than 25% of the patient's bone marrow be involved with tumor. Bone marrow involvement is determined from a bone marrow biopsy, ideally performed within 6 wk of therapy. Ibritumomab tiuxetan should not be administered to patients with impaired bone marrow reserves, including those who have been given prior myelotoxic therapies with autologous bone marrow transplantation or peripheral blood stem cell rescue and those with hypocellular bone marrow, a history of failed stem cell collection, or prior external-beam radiation to more than 25% of the active marrow. The patient's platelet count and absolute neutrophil count must be at least 100,000 cells/mm^3 and 1,500 cells/mm^3, respectively.

^{90}Y-Ibritumomab tiuxetan is contraindicated in patients with known type 1 hypersensitivity or anaphylactic reactions to murine proteins or to any component of this product, including yttrium chloride and indium chloride. Although human antimurine antibody (HAMA) and human antichimeric antibody responses to ibritumomab tiuxetan therapy were rare (<2%) during clinical trials, patients who have received murine proteins should be screened for

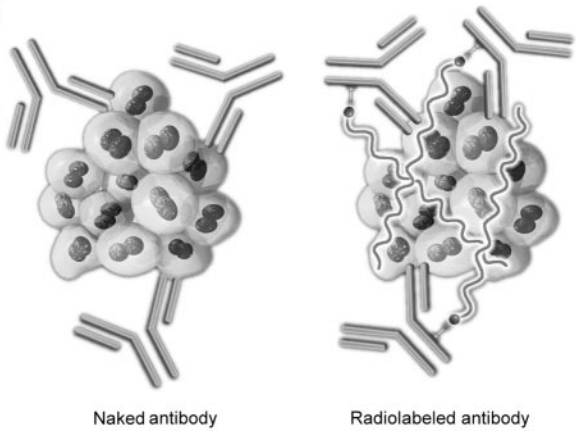

FIGURE 2. Radioimmunotherapy uses targeting of monoclonal antibody to produce crossfire effect with radioimmunoconjugate.

HAMA. Studies on patients with evidence of HAMA have not been conducted, and they may be at greater risk of allergic or serious hypersensitivity reactions during ^{90}Y-ibritumomab tiuxetan administration (*12*).

IMAGING AND THERAPY PROTOCOL

The ibritumomab tiuxetan protocol is performed by a multidisciplinary team of health-care professionals (Table 1) over 7–9 d (Fig. 3). Coordination of activities and personnel is essential to the success of this protocol and includes the following steps:

- Five days before infusion of ^{111}In-ibritumomab tiuxetan, the hematologist or oncologist identifies an appropriate patient and refers the patient to nuclear medicine. The nuclear medicine physician confirms patient appropriateness (meets inclusion criteria) and implements the therapy protocol, which includes patient scheduling (infusions and imaging); dose procurement; and, as necessary, coordination of radiation oncology personnel for ^{90}Y-ibritumomab tiuxetan infusion. The oncology nurse schedules the rituximab infusions and the patient's post-treatment follow-up appointments with the hematologist or oncologist. The utilization review and patient billing department obtains authorization for treatment from the patient's insurance carrier.
- On day 1, the patient receives rituximab, 250 mg/m^2, over 2–4 h followed within 4 h by 185 MBq (5 mCi) ^{111}In-ibritumomab tiuxetan.
- Day 1 or 2 (2–24 h), anterior and posterior whole-body images are obtained.
- Day 3 or 4 (48–72 h), anterior and posterior whole-body images are obtained.
- Day 5 or 6 (90–120 h), optional anterior and posterior whole-body images are obtained.

TABLE 1
Health-Care Team for Ibritumomab Tiuxetan Therapy

Health-care professional	Roles and responsibilities
Hematologist/oncologist	• Patient identification and assessment (including pregnancy) • Patient education, consent • Prescription of rituximab dose • Patient follow-up and monitoring
Oncology nurse	• Coordination of patient scheduling with nuclear medicine, infusion clinic, and radiation oncology (as necessary) • Patient education • Patient monitoring before and after infusion
Nuclear medicine physician	• Review of pertinent patient information • Prescription of ^{111}In- and ^{90}Y-ibritumomab tiuxetan doses • Patient education and consent • Interpretation of whole-body images • Calculation and administration of therapy dose • Final procedure reporting and documentation
Nuclear medicine technologist/ nuclear radiopharmacist	• Interaction with oncology nurse; coordination of patient scheduling • Procurement and preparation of imaging and therapy doses • Safe and appropriate receipt, handling, administration, and disposal of radiopharmaceuticals • Patient education • Whole-body imaging of patients
Commercial radiopharmacist	• Receipt of orders; confirmation of patient dose • Order placement with supplier for cold kits and yttrium • Order placement for ^{111}In • Radiolabeling of drugs with ≥95% tagging efficiency • Delivery of unit dose to clinical site
Radiation safety officer	• Oversight of safe handling, administration, and disposal of radiopharmaceuticals according to state or federal guidelines
Utilization review/patient billing staff	• Confirmation of appropriate clinical indications • Acquisition of authorization from third-party payers • Follow-up (as necessary) on reimbursement issues
Radiation oncologist	• Review of pertinent patient information • Prescription of ^{90}Y-ibritumomab tiuxetan dose • Patient education • Calculation and administration of therapy dose • Final procedure reporting and documentation
Radiation oncology nurse	• Coordination of patient scheduling with nuclear medicine and infusion clinic • Patient education • Patient monitoring before and after infusion

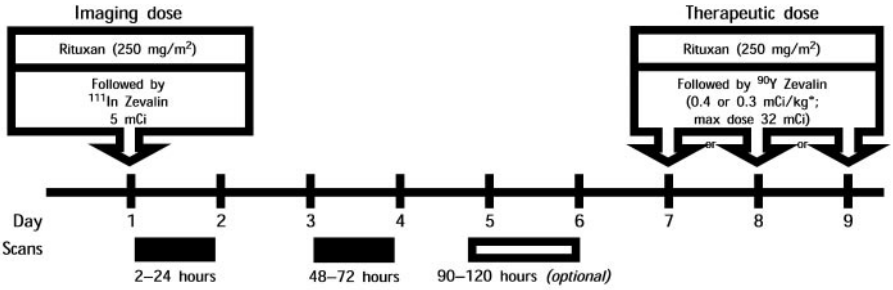

FIGURE 3. Imaging and therapy protocol is administered over 7–9 d.

- Day 7, 8, or 9, the patient receives a therapeutic infusion of rituximab, 250 mg/m^2, over 2–4 h followed within 4 h by 14.8 MBq/kg (0.4 mCi/kg) ^{90}Y-ibritumomab tiuxetan (11.1 MBq/kg [0.3 mCi/kg] for patients with platelet counts of between 100,000/mm^3 and 149,000/mm^3), to a maximum dose of 1,184 MBq (32 mCi).

RADIOPHARMACEUTICAL ACQUISITION, CALIBRATION, AND STORAGE

Ibritumomab tiuxetan is radiolabeled by most commercial radiopharmacies and is delivered to the hospital or clinic as a unit dose (*20*). Depending on the availability of yttrium chloride, the therapy protocol begins on a Tuesday or Wednesday, as determined by the site.

Ordering ibritumomab tiuxetan requires a single phone call to the radiopharmacy. Specific information to provide to the radiopharmacist includes infusion dates (Tuesdays or Wednesdays only), required activity, delivery time (in most cases, 11:30 AM to 2:00 PM), and the patient's weight and platelet count. In scheduling unit dose delivery, it is important to remember that the time between rituximab infusion and ibritumomab tiuxetan infusion should not exceed 4 h. If the patient is not available for immediate infusion, ibritumomab tiuxetan should be refrigerated (2°C–8°C). Once compounded, ^{111}In-ibritumomab tiuxetan has a shelf life of 12 h and ^{90}Y-ibritumomab tiuxetan has a shelf life of 8 h.

DOSE CALCULATION AND ADMINISTRATION

The standard adult ^{111}In-ibritumomab tiuxetan imaging dose is 185 MBq (5 mCi). Unlike radiopharmaceuticals, such as ^{131}I, that have a highly variable clearance rate necessitating assessment of biologic clearance to determine an appropriate therapy dose, ^{90}Y-ibritumomab tiuxetan does not require individual dosimetry. Because clearance varies little between patients, the dose is calculated on the basis of body weight and platelet count (*21*). The initial clinical trials included complex organ dosimetry using a surrogate radionuclide, ^{111}In-ibritumomab tiuxetan, before treatment with ^{90}Y-ibritumomab tiuxetan to estimate radiation absorbed doses to normal organs and bone marrow (*21*). The amount of radiation absorbed by normal organs (≤20 Gy [2,000 rad]) and red bone marrow (≤3 Gy [300 rad]) was determined using quantitative imaging with ^{111}In-ibritumomab tiuxetan and the MIRDOSE3 software program (Radiation Internal Dose Information Center) (*22*,*23*). Dosimetry results for 179 patients across 4 trials confirmed that in patients with relapsed low-grade, follicular, or transformed B-cell NHL and rituximab-refractory NHL, individualized quantitative radiation dosimetry is not necessary for safe treatment with ^{90}Y-ibritumomab tiuxetan using standard weight-based doses (*22*,*24*). The ^{90}Y-ibritumomab tiuxetan weight-based dose calculation is 11.1 MBq/kg (0.3 mCi/kg) for platelet counts of between 100,000 and 149,000 cells/mm^3 and 14.8 MBq/kg (0.4 mCi/kg) for platelet counts ≥ 150,000 cells/mm^3. The maximum therapy dose is 1,184 MBq (32 mCi) (*21*). ^{90}Y-Ibritumomab tiuxetan should not be administered to patients with platelet counts < 100,000 cells/mm^3.

Guidelines published by the manufacturer of the dose calibrator describe the assay procedure for ^{111}In-ibritumomab tiuxetan, a pure γ-emitter. However, like the recommendation for assaying ^{89}Sr, to accurately assay ^{90}Y it is recommended that the calibration settings for the dose calibrator be qualified using ^{90}Y and corrected for different geometries (liquid volumes and receptacles).

Before the administration of radiolabeled ibritumomab tiuxetan, patients are given a dose of rituximab, 250 mg/m^2. In most cases, the rituximab infusion is administered in the oncologist's office or infusion clinic. Rituximab is administered to saturate readily accessible CD20 sites on B cells in the circulation and in the spleen, thus improving the biodistribution of the ibritumomab tiuxetan (*25*,*26*). The concept of saturation can be compared with the flushing dose of unlabeled vitamin B_{12} used in Schilling tests. Additionally, rituximab has an intrinsic cytotoxicity of its own, and some of the rituximab binds to tumor cells, initiating tumor cell death through immune-mediated processes (antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, or apoptosis), potentially increasing the antitumor effects of the entire treatment protocol.

Patient preparation is minimal for ibritumomab tiuxetan administration. In many cases, the patient arrives from the oncologist's office or infusion clinic with an indwelling catheter in place. Hickman catheters and porta catheters may be used for infusion; however, the location of the catheter should be noted on the whole-body images to assist the nuclear medicine physician in correctly interpreting possible increased activity at the site of the catheter. Once

venous access has been confirmed, the radiolabeled ibritumomab tiuxetan is administered slowly, over 10 min, through a low-protein-binding 0.22-μm filter between the unit dose and the patient. The filter removes any translucent particles from the antibody protein solution of ^{111}In- and ^{90}Y-ibritumomab tiuxetan. To minimize residual activity on the filter, the filter is wet with 0.9% sodium chloride before use. To avoid restricted flow or "filter lock," air is not allowed to pass through the wet filter at any time during syringe setup or radionuclide infusion. The dose volume is 10 mL of ^{111}In-ibritumomab tiuxetan and 4–8 mL of ^{90}Y-ibritumomab tiuxetan. After infusion, the intravenous tubing, including the filter, is flushed with 10–20 mL of 0.9% sodium chloride to ensure complete delivery of the dose to the patient. Ibritumomab tiuxetan should not be administered concurrently with other intravenous solutions or medications. It should never be administered as a bolus. The infusion site should be continually assessed during dose administration to avoid extravasation of the dose.

IBRITUMOMAB TIUXETAN IMAGING AND THERAPY PROTOCOL

Whole-body imaging with ^{111}In-ibritumomab tiuxetan is performed as an additional safety measure to confirm normal biodistribution of the antibody (Table 2). Biodistribution is assessed by visual examination of anterior and posterior whole-body images obtained at 2–24 h and 48–72 h after the injection. To resolve ambiguities, a third whole-body image can be obtained at 90–120 h. Expected biodistribution is described as easily detectable uptake in the blood pool and moderately high to high uptake in the normal liver and spleen on the initial images. Uptake in the blood pool will decrease in the later images. Uptake in the lungs, kidneys, and urinary bladder should remain low at all times. Occasional localization to lymphoid aggregates in the bowel wall has been reported. Tumor uptake may be seen as areas of increased intensity in soft tissue and as areas of increased or decreased intensity in tumor-bearing areas of normal organs (Fig. 4). Of note, a lack of tumor uptake on early or delayed images does not disqualify the patient from ^{90}Y-ibritumomab tiuxetan therapy. If the whole-body images demonstrate the expected biodistribution, the decision to administer ^{90}Y-ibritumomab tiuxetan will be made by the nuclear medicine physician. Altered biodistribution is rare, and patients with altered biodistribution should not be treated with ^{90}Y-ibritumomab tiuxetan. Altered biodistribution is defined as blood-pool activity not visualized on the first image, lung or kidney uptake more intense than liver uptake on the second image, or diffuse intense uptake in the bowel comparable to uptake in the liver on the second image. When altered biodistribution is suspected, whole-body images should be obtained at 90–120 h to rule out delayed clearance or other abnormalities. The nuclear medicine physician should discuss any altered biodistribution findings with the referring physician to determine whether to proceed with the therapeutic ^{90}Y-ibritumomab tiuxetan.

TABLE 2
Data Acquisition Parameters

Acquisition type	Parameter
Whole body	Dual- or single-head gamma camera Medium-energy collimators 171 and 245 keV (15%–20% window) 256 × 1,024 matrix Camera speed (time dependent) • 10 cm/min (20-min scan) at 2–24 h • 7–10 cm/min (30-min scan) at 48–72 h • 5–7 cm/min (40-min scan) at 90–120 h
Planar (spot)	256 × 256 matrix 5 min/500K images

SAFETY OF IBRITUMOMAB TIUXETAN

The ibritumomab tiuxetan regimen is not associated with the adverse events that are often associated with chemotherapy, such as hair loss, severe mucositis, and persistent nausea or vomiting. The nonhematologic adverse events (e.g., fatigue, nausea, fever, and chills) that do occur are mostly grade 1 or 2 and are most often related to the rituximab infusions rather than to the ^{90}Y-ibritumomab tiuxetan injection (*27*). Hematologic toxicity occurs to some extent in all patients. The nadirs in the blood cell counts occur most often at approximately 7–9 wk after treatment but may occur earlier. In some cases, platelet or red blood cell transfusions may be necessary, as well as hospitalization for infection in patients with low leukocyte counts. Hematopoietic growth factors may be required to stimulate bone marrow to increase its production. The main predictor of hematologic toxicity in clinical trials was the patient's bone marrow reserves (e.g., lymphoma bone marrow involvement or pretreatment platelet count). There was no significant correlation between the grade of hematologic toxicity and pharmacokinetic or dosimetric measures, including blood half-life, blood residence time, red marrow radiation dose, and total body dose (*24*).

The radiation risk to health-care personnel from handling ^{111}In- and ^{90}Y-ibritumomab tiuxetan can be kept as low as reasonably achievable by minimizing the duration of exposure, maximizing distance from the source, and using appropriate shielding (*28*). Lead or tungsten provides adequate shielding for ^{111}In, but for an energetic pure β-emitter such as ^{90}Y, 1-cm plastic or acrylic, rather than lead shielding, is recommended (*21*). Additionally, exposure can be further minimized by using commercially available plastic or acrylic shielding plus lead or tungsten shielding, which is designed to provide greater protection from the potential exposure of β-radiation and bremsstrahlung. Radiation safety guidelines for each institution will provide health-care personnel with the basic radiation safety procedures for the safe handling, calibration, administration, and disposal of pure β-emitters such as ^{90}Y (*21*).

Because ^{90}Y is a pure β-emitter, the radiation risk to the patient's family and others is minimal, making it possible to routinely use ^{90}Y-ibritumomab tiuxetan on an outpatient

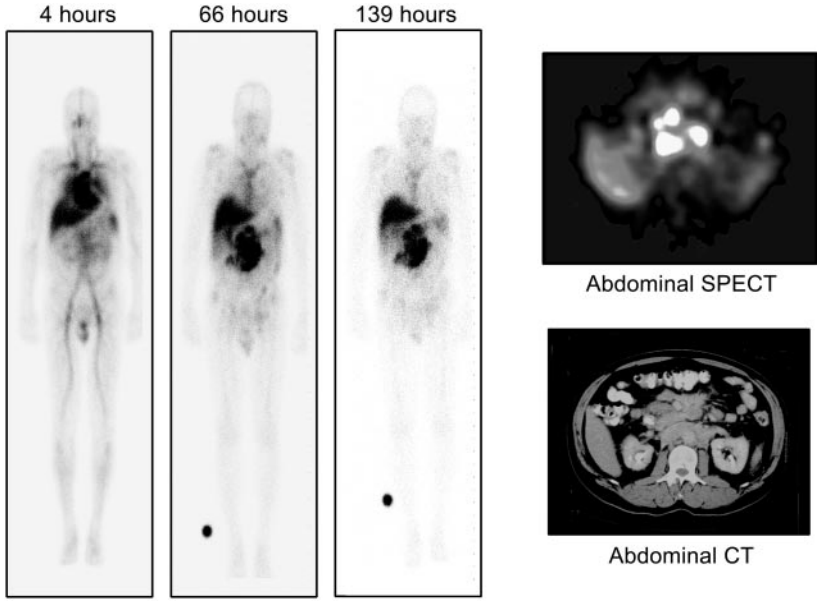

FIGURE 4. Serial whole-body anterior gamma camera images after injection of ^{111}In-ibritumomab tiuxetan illustrate normal biodistribution, including blood pool (diminishes over time), liver, spleen, and bulky tumor. Abdominal SPECT and CT views correlate uptake with abdominal adenopathy.

basis. The calculated potential dose of radiation to others exposed to a patient treated with ^{90}Y-ibritumomab tiuxetan is less than 0.01 mSv (1 mrem) (*21*). In the clinical trials, urinary excretion of radiation was minimal, only 7.3% (±3%) over 7 d (*29*). With the maximum dose of 1,184 MBq (32 mCi), this would equate to a urinary excretion of 85 MBq (2.3 mCi) over 1 wk, or activity per urination in the kilobecquerel (microcurie) range (*21*). In another prospective study, 13 family members who were in closest contact with patients treated with ^{90}Y-ibritumomab tiuxetan wore personal dosimeters (DoseGUARD Plus; AEA Technology QSA Inc.) for 7 d (*30*). The family members were instructed to avoid body wastes from the patients, but no other precautions were given. The median deep-dose radiation exposure was 0.035 mSv (3.5 mrem) over 7 d, which is in the range of normal background radiation.

PATIENT DISCHARGE INSTRUCTIONS

When pure β-emitters are used, patients require minimal discharge instructions to minimize exposure to others (*12*). For the first 7 d after outpatient administration of ^{90}Y-ibritumomab tiuxetan therapy, patients should wash their hands thoroughly after using the toilet, avoid transfer of body fluids (saliva, blood, urine, or stool), clean up any spilled urine and dispose of any material contaminated with body fluids so that others will not inadvertently handle it, and use condoms for sexual relations. For up to 12 mo after treatment, patients should use effective contraceptive methods.

Health-care personnel should follow standard universal precautions for body wastes, including blood and urine, for any patient admitted to the hospital after treatment with ^{90}Y-ibritumomab tiuxetan. The gastrointestinal contents are minimal, and there is no risk of dangerous levels of radioactivity in normal amounts of blood from, for example, menstruation, cuts, or hemorrhoids.

CODING AND REIMBURSEMENT

For 2003, the Centers for Medicare and Medicaid Services (CMS) created 2 new codes: G0273, to encompass administration of ^{111}In-ibritumomab and whole-body diagnostic radionuclide scanning, and G0274, for therapeutic administration of ^{90}Y-ibritumomab tiuxetan (Table 3). In the latest Program Memorandum for Intermediaries and Carri-

TABLE 3
Medicare Coding and Payment for 2003

Product/procedure	Code	Description	APC	Payment*	Professional component†
^{111}In-Ibritumomab tiuxetan plus scan	G0273	Pre–radiopharmaceutical treatment planning, NHL	0718	$2,750	2003 physician fee schedule, $45.25
^{90}Y-Ibritumomab tiuxetan administration	G0274	Radiopharmaceutical treatment, NHL	0725	$20,000	2003 physician fee schedule, $108.88

*Payment subject to institution's Wage Index Adjustment.

†Average allowable from physician's fee schedule.

APC = ambulatory payment classification.

TABLE 4
Private Payer Coding for 2003

Product/procedure	Code	Description	Payment
^{111}In	A9522	^{111}In-Ibritumomab tiuxetan	% of AWP or invoice
Imaging	78802	Radiopharmaceutical localization of tumor, whole body	Fee schedule, contracted rate, % of charge
^{90}Y-Ibritumomab tiuxetan administration	A9523	^{90}Y-Ibritumomab tiuxetan per mCi based on 40 mCi/dose	% of AWP or invoice
Yttrium administration	79400	Radiopharmaceutical therapy, nonthyroid, nonhematologic	Fee schedule, contracted rate, % of charge

AWP = average wholesale price.

ers, dated January 6, 2003 (CMS publication 60AB; transmittal A-02-129, XVII), the G0273 code is defined as including the administration of the radiopharmaceutical and performance of all scans regardless of the number of images or number of days required to perform the imaging. The payment amount for G0273 and G0274 includes both the procedure and the radiopharmaceutical. For diagnostic administration of ^{111}In-ibritumomab tiuxetan, current procedural terminology (CPT) codes for diagnostic administration of radiopharmaceuticals (78990 and 78999) and diagnostic scanning (78800–78803) should not be reported. For therapeutic administration of ^{90}Y-ibritumomab tiuxetan G0274, CPT codes for therapeutic administration of radiopharmaceuticals (79900), radiopharmaceutical therapy (79100, 79400), and infusion or instillation of radioelement solution (77750) should not be reported. Physician offices should use codes A9522 and 78802 of the Health Care Financing Administrators Common Procedure Coding System for diagnostic administration and scanning of ^{111}In-ibritumomab tiuxetan and A9523 and 79400 for therapeutic administration of ^{90}Y-ibritumomab tiuxetan (Table 4). Providers are instructed to bill for the number of units consumed by the radiopharmacy to prepare ibritumomab tiuxetan doses (5 units [mCi] ^{111}In; 40 units [mCi] ^{90}Y) that will subsequently be billed to the provider. Facilities not paid under the outpatient prospective payment system are directed to use current billing practices.

The coding instructions provided by CMS indicate only a method to receive payment for ibritumomab tiuxetan if it is covered by Medicare. They do not represent a determination that the Medicare program covers ibritumomab tiuxetan. CMS continues to perform a national coverage determination for ibritumomab tiuxetan to ensure that the radioimmunotherapy is appropriately used in the Medicare population.

The "take-home" message to ensure appropriate reimbursement, regardless of the patient's health-care plan, is to carefully screen the patient for appropriate clinical indications, obtain preauthorization from the patient's health-care provider, and accurately code the imaging and therapy procedure. Updated information is available on the Society of Nuclear Medicine Web site (http://www.snm.org/policy/links.html [select "reimbursement"]).

CONCLUSION

^{90}Y-Ibritumomab tiuxetan is a radioimmunotherapy that results in high overall or complete response rates in patients with relapsed or refractory indolent, follicular, or CD20+ transformed NHL. A multidisciplinary team of health-care professionals performs the imaging and therapy protocol over 7–9 d. Ibritumomab tiuxetan is generally well tolerated. Hematologic toxicity, which occurs to some extent in all patients, is transient and reversible in most cases. Because ^{90}Y is a pure β-emitter, ^{90}Y-ibritumomab tiuxetan can be administered in an outpatient setting with minimal disruption to the patient's normal activities and quality of life.

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