

Radiation Safety Considerations With Yttrium 90 Ibritumomab Tiuxetan (Zevalin)

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Radioimmunotherapy is a recently approved treatment modality for non-Hodgkin's lymphoma that enables physicians to target cytotoxic localized radiation to tumor sites without using external-beam sources. Because it uses a pure beta emitter for therapy, ^{90}Y ibritumomab tiuxetan can be safely and routinely administered in an outpatient procedure, with few discharge instructions, and minimal risk of radiation exposure to a patient's family and acquaintances. Safety precautions for medical professionals administering ^{90}Y ibritumomab tiuxetan are universal precautions, with the

IBRITUMOMAB is a murine monoclonal antibody that is linked to the second-generation chelator tiuxetan, which binds to radiometals (yttrium 90 for therapeutic doses or indium 111 for imaging doses) with high affinity, making the resultant radioimmunoconjugates highly stable. It is important that nuclear medicine physicians understand the components of this regimen to effectively implement the appropriate radiation safety measures. Yttrium 90 ibritumomab tiuxetan is routinely and safely administered in an outpatient procedure, with few discharge instructions, and minimal risk of radiation exposure to a patient's family and acquaintances. Safety precautions for medical professionals administering ^{90}Y ibritumomab tiuxetan are universal precautions, with the addition of acrylic shielding for the administration of radiolabeled doses.

RADIATION SAFETY CONSIDERATIONS

Indium 111-labeled agents have been used in nuclear medicine imaging for decades. For the imaging dose of ^{111}In ibritumomab tiuxetan, no precautions are necessary other than those that have routinely been used in nuclear medicine diagnostic procedures. Because ^{90}Y is a pure beta

emitter, it requires less restrictive radiation safety procedures¹⁻³ than those required for gamma emitters such as ^{131}I (Tables 1 and 2).

addition of acrylic shielding for the administration of radiolabeled doses. The risk of radiation exposure to healthcare workers and family members is minimal. The primary route for biologic elimination of ^{90}Y ibritumomab tiuxetan is through the urine. While radiation safety instructions are not required according to the relevant patient release criteria, basic instructions to the patient and family may be valuable to further minimize the risk of radiation exposure and help alleviate patient and family concerns.

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emitter, it requires less restrictive radiation safety procedures¹⁻³ than those required for gamma emitters such as ^{131}I (Tables 1 and 2).

EXTERNAL RADIATION DOSES TO WORKERS

As mentioned above, ^{90}Y is a pure beta emitter with a maximum energy of 2.3 MeV (Table 3). In vivo, the mean effective path length of ^{90}Y in soft tissue is approximately 5 mm, or approximately 100 to 200 cell diameters. This means that 90% of the energy is absorbed within a sphere with a 5-mm radius.⁴ Because ^{90}Y is a penetrating beta emitter, precautions must be taken to minimize the external skin dose to personnel (Fig 1).⁵ Beta radiation, like that from ^{90}Y , can be shielded effectively with plastic or glass (Fig 2). The maximum range of the beta particles emitted by ^{90}Y is only 4.9 mm in glass and 9.2 mm in plastic.⁶ The dose rate from handling a standard dose of ^{90}Y ibritumomab tiuxetan administered with an acrylic-shielded syringe has been measured at 320 mrem/h.⁷

The lead or tungsten syringe shields commonly used in nuclear medicine are not appropriate for use in shielding ^{90}Y . The bremsstrahlung generated by the interaction of the high-energy beta particles of ^{90}Y with high-atomic-number materials, such as lead and tungsten, may increase the doses of radiation rather than reduce them. Plastic syringe shields specifically designed to shield beta radiation are available from radiation protection or nuclear medicine supply vendors, and should be used when administering ^{90}Y ibritumomab tiuxetan (Fig 3).

Beta radiation from ^{90}Y cannot penetrate outside of the patient's body; therefore, bremsstrahlung from the interaction of the beta particles with the patient's tissues is the only theoretical source of external exposure to other persons after ^{90}Y ibritumomab tiuxetan has been administered. It has

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**Table 1. ^{90}Y Ibritumomab Tiuxetan
Patient Release Instructions**

<ul style="list-style-type: none"> ● For 3 days after treatment: <ul style="list-style-type: none"> Clean up spilled urine and dispose of body-fluid-contaminated material so that others will not inadvertently handle it (ie, flush down toilet or place in plastic bag in household trash) Wash hands thoroughly after using the toilet ● For 1 week after treatment: <ul style="list-style-type: none"> Use condoms for sexual relations ● For 1 year after treatment: <ul style="list-style-type: none"> Avoid pregnancy Mothers discontinue breastfeeding infants and use formula instead of breast milk

been shown both by calculation and by measurements taken during clinical trials that the whole body external radiation doses to radiation workers and patients' family members during and immediately after administration of the ibritumomab tiuxetan regimen are very low, as discussed below.^{8,9}

Dose Calibration

Because ^{111}In -labeled radiopharmaceuticals are routinely used in hospitals and medical centers, new protocols for verifying the doses of ^{111}In need not be developed. Dose calibrators, available commercially, normally have a setting or dial specifically for ^{111}In . Depending on the model, a calibrator may or may not have a specific setting or dial for ^{90}Y . Dose measurements for beta emitters such as ^{90}Y are highly dependent on the geometry. The dose calibrator used for beta dose assay must be calibrated for the same geometry as that used by the radiopharmaceutical manufacturer to deliver the dose to the facility (eg, 10-mL syringe), regardless of the dial setting, because the dial in the manufacturer's instruction manual might not have been determined with the same geometry that will be used for patients in the facility. If the dose of ^{90}Y ibritumomab tiuxetan is supplied by a licensed 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 prescriptions, with no correction required for differing volumes in the calibrated 10-mL syringe.² Medical facilities need only use this calibrated dial setting and simply measure and record the activity of ^{90}Y ibritumomab tiuxetan, regardless of the volume in the supplied syringe. To calibrate the dose calibrator for the specific geometry, the user may request that the radiophar-

macy delivery a dose in a specific geometry (eg, ^{90}Y ibritumomab tiuxetan 8 mL in a 10-mL syringe), and adjust dial or setting for future verification. If the ^{90}Y is measured in-house instead of by an outside radiopharmacy, the dose calibrator should be calibrated for ^{90}Y by using the actual geometry of the specific administered dose.

Authorized Users, Written Directives

The US Nuclear Regulatory Commission requires that written directives be completed before the administration of ^{90}Y ibritumomab tiuxetan. An authorized user physician must sign the written directive before administering the dose. The authorized user physician must be on the facility's license or be approved by the facility's broad-scope radiation safety committee for 10CFR35.300 use. An authorized user physician who is licensed or approved only for uptake, dilution, and excretion studies (10CFR35.100), imaging and localization studies (10CFR35.200), or manual brachytherapy (10CFR35.400) must be reviewed and approved by the US Nuclear Regulatory Commission, agreement state authorities, or the radiation safety committee of a broad-scope licensee before she or he can become an authorized user physician for ^{90}Y ibritumomab tiuxetan.

Patient Release

The ibritumomab tiuxetan regimen is routinely and safely performed as an outpatient procedure, with minimal risk for patients and those in close contact with them. Clinical trial data and laboratory calculations have shown that radiation exposure from a patient treated with ^{90}Y ibritumomab tiuxetan is very small, within the range of background radiation.^{8,9}

Table 2. ^{131}I Tositumomab Patient Release Instructions

Both oral and written instructions should be provided informing patients of the following:
For 4 to 7 days after administration
<ul style="list-style-type: none"> ● Sleep in a separate bed (≥ 6 feet apart) ● Keep ≥ 6 feet from children and pregnant women ● Do not take long trips ● Limit time spent in public places ● Use a separate bathroom ● Sit while urinating ● Wash hands frequently ● Drink plenty of liquids ● Use separate eating utensils ● Wash laundry separately, avoid using disposable items ● Avoid sexual contact

Data from Siegel et al² and Bexxar prescribing information.³

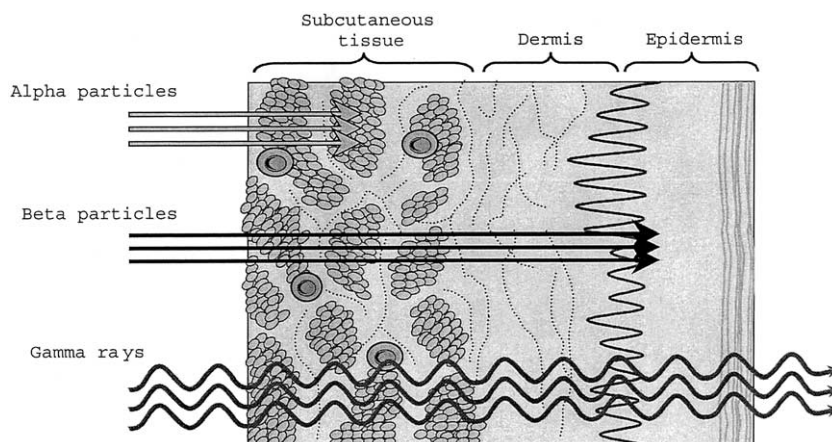


Fig 1. Penetration of particulate and electromagnetic radiation. (Adapted from Wootton R (ed), *Radiation Protection of Patients*, 1993. Reprinted with permission from Cambridge University Press.⁵)

Zanzonico et al⁸ have calculated the bremsstrahlung exposure from various beta emitters, establishing the term “specific bremsstrahlung constant” to describe the radiation dose rate of bremsstrahlung from high-energy beta interactions with specified media. The specific bremsstrahlung constants were used to calculate dose limits (in millicuries) for patient release from medical confinement according to US Nuclear Regulatory Commission Guide 8.39. The authors concluded that hospitalization of a patient treated with ⁹⁰Y would be required only if the radioactivity administered exceeded 38,500 mCi, a dose that exceeds the maximum 32 mCi administered with ⁹⁰Y ibritumomab tiuxetan by three orders of magnitude.⁸ This calculation was made assuming no biologic elimination of the radionuclide, no tissue (patient’s body) self-absorption, and an occupancy factor of 0.25 at a distance of 1 m from a dosed patient.

The conclusion that the risk of radiation exposure from a patient treated with ⁹⁰Y ibritumomab tiuxetan is very small is further supported by

measurements obtained in clinical trials with ⁹⁰Y ibritumomab tiuxetan. Using personal dosimeters, Wiseman et al⁹ measured radiation exposure in 13 family members of patients who had been treated with ⁹⁰Y ibritumomab tiuxetan. Their research showed that the radiation exposure from a patient treated with ⁹⁰Y ibritumomab tiuxetan could not be distinguished from that resulting from background radiation. The median deep-dose equivalent was 3.4 mrem (total accumulation over 7 days), and the median dose rate measured at 1 m from the patient was 0.3 mrem/hour.⁹

Patient Instructions

Written radiation safety instructions are not required according to the patient release criteria in 10CFR35.75 and Regulatory Guide 8.39, because of the very low risk of radiation exposures to other

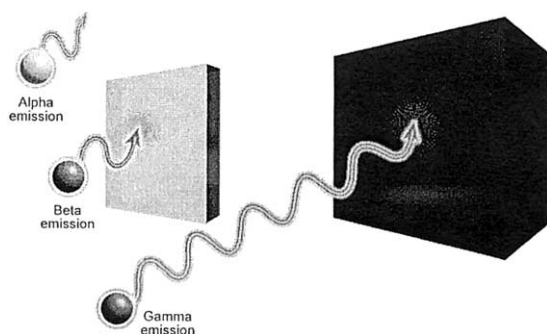


Fig 2. Radiation safety issues are less with pure beta decay (⁹⁰Y).

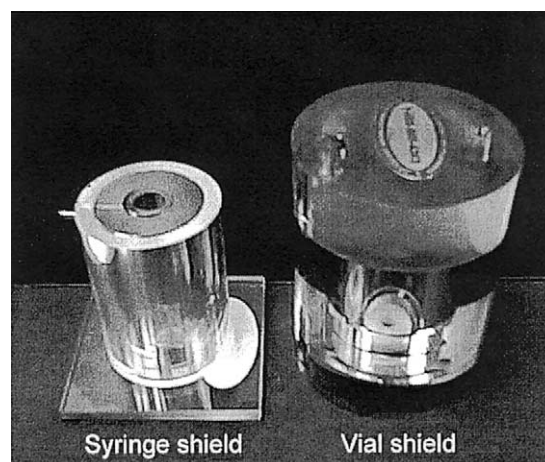


Fig 3. Acrylic syringe and vial shields for pure beta emitters (⁹⁰Y).

Table 3. Properties of Radionuclides (⁹⁰Y and ¹³¹I)

Radio-isotope	Physical Half-Life (Hours)	Decay Type	Particle Energy (MeV)	Primary Gamma Energy (MeV)	Mean Particle Path Length (mm)
⁹⁰ Y	64	Beta	2.31	None	5.3
¹³¹ I	193	Gamma, beta	0.61	0.364	0.8

persons who have contact with the patient after the administration of ⁹⁰Y ibritumomab tiuxetan. Patients and their family members, however, will often have questions about potential post-administration radiation exposure. It is important to understand the biokinetics of ⁹⁰Y ibritumomab tiuxetan so that appropriate recommendations can be made.

Urinary excretion is the main route of biologic elimination of ⁹⁰Y ibritumomab tiuxetan, with a mean $7.3\% \pm 3.2\%$ of an administered dose excreted in the urine over a 7-day period.¹⁰ The excreted fraction of a maximum dose of 32 mCi is about 3 mCi, which is in the range of tens of microcuries per void of urine.¹¹ The effective half-life of ⁹⁰Y ibritumomab tiuxetan in the bloodstream is 30 hours. The amount of radioactivity in a urine or blood sample is not likely to cause substantial radiation doses to laboratory personnel. However, caution must be taken to avoid ingestion or skin contamination. Medical personnel should take the standard universal precautions (wearing gloves and a laboratory coat or disposable gown) when handling a patient's body fluids. Patients should be advised to take precautions, including cleaning up any spilled body fluids (eg, urine) and

washing their hands thoroughly after using the toilet (Table 1). These precautions should be observed for 3 days after the administration of ⁹⁰Y ibritumomab tiuxetan. Patients should also be advised to use condoms for sexual intercourse for 7 days after administration and to avoid pregnancy for 12 months after administration. Mothers should be advised to discontinue nursing and to feed their infants formula instead of breast milk.¹

Because it uses a pure beta emitter, ⁹⁰Y ibritumomab tiuxetan can be safely and routinely administered in an outpatient procedure. The risk of radiation exposure to healthcare workers and family members is minimal. The primary route for biologic elimination of ⁹⁰Y ibritumomab tiuxetan is through the urine. Standard universal precautions, which should already be in place in healthcare facilities, should be sufficient to prevent contamination of personnel. While radiation safety instructions are not required according to the relevant patient release criteria, basic instructions to the patient and family may be valuable to further minimize the risk of radiation exposure and help alleviate patient and family concerns. Patients should be advised to: for 3 days after the administration of ⁹⁰Y ibritumomab tiuxetan, clean up any spilled body fluids and wash their hands thoroughly after using the toilet; for 7 days after administration, use condoms for sexual intercourse; and, for 12 months after administration, avoid pregnancy. Mothers should be advised to discontinue nursing and to feed their infants formula instead of breast milk.

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