High-Dose ^{131}I-Tositumomab (Anti-CD20) Radioimmunotherapy for Non-Hodgkin's Lymphoma: Adjusting Radiation Absorbed Dose to Actual Organ Volumes

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Radioimmunotherapy (RIT) using ^{131}I-tositumomab has been used successfully to treat relapsed or refractory B-cell non-Hodgkin's lymphoma (NHL). Our approach to treatment planning has been to determine limits on radiation absorbed dose to critical nonhematopoietic organs. This study demonstrates the feasibility of using CT to adjust for actual organ volumes in calculating organ-specific absorbed dose estimates. **Methods:** Records of 84 patients who underwent biodistribution studies after a trace-labeled infusion of ^{131}I-tositumomab for RIT (January 1990 and April 2003) were reviewed. Serial planar γ-camera images and whole-body NaI probe counts were obtained to estimate ^{131}I-antibody source-organ residence times as recommended by the MIRD Committee. The source-organ residence times for standard man or woman were adjusted by the ratio of the MIRD phantom organ mass to the CT-derived organ mass. **Results:** The mean radiation absorbed doses (in mGy/MBq) for our data using the MIRD model were lungs = 1.67; liver = 1.03; kidneys = 1.08; spleen = 2.67; and whole body = 0.3; and for CT volume-adjusted organ volumes (in mGy/MBq) were lungs = 1.30; liver = 0.92; kidneys = 0.76; spleen = 1.40; and whole body = 0.22. We determined the following correlation coefficients between the 2 methods for the various organs: lungs, 0.49 (P = 0.0001); liver, 0.64 (P = 0.004); kidneys, 0.45 (P = 0.0004); spleen, 0.22 (P = 0.0001); and whole body, 0.78 (P = 0.0001), for the residence times. For therapy, patients received mean ^{131}I administered activities of 19.2 GBq (520 mCi) after adjustment for CT-derived organ mass compared with 16.0 GBq (433 mCi) that would otherwise have been given had therapy been based only using standard MIRD organ volumes—a statistically significant difference (P = 0.0001). **Conclusion:** We observed large variations in organ masses among our patients. Our treatments were planned to deliver the maximally tolerated radiation dose to the dose-limiting normal organ. This work provides a simplified method for calculating patient-specific radiation doses by adjusting for the actual organ mass and shows the value of this approach in treatment planning for RIT.

Key Words: non-Hodgkin's lymphoma; radioimmunotherapy; internal dosimetry; MIRD models; patient-specific dosimetry

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Non-Hodgkin's lymphoma (NHL) affects nearly 12 per 100,000 people in the United States (*1*). Radioimmunotherapy (RIT) with ^{131}I-tositumomab (anti-CD20) antibody was introduced to improve on the results of modern radiation therapy and combination chemotherapy (*2*,*3*) and to minimize the toxicities associated with transplant conditioning regimens. RIT takes advantage of the lineage-restricted expression of the CD20 antigen on B cells and on B-cell NHL (*4*) and the inherent radiosensitivity of lymphoid tissue—while minimizing normal tissue toxicity by targeting antigen-positive cells. The clinical utility of high-dose RIT for lymphoma is well established (*5–7*).

Biodistribution of ^{131}I-tositumomab in patients shows prolonged blood clearance and related long residence in the blood pool and normal organs, including liver, spleen, lungs, and kidneys. The average whole-body clearance half-time is approximately 90 h. Although the aim of RIT is to irradiate tumor, the normal organs and tissues receive significant radiation dose from circulating radioactivity. In keeping with other treatment modalities such as chemotherapy and external-beam radiotherapy, it is important to achieve the best possible therapeutic ratio, delivering the highest possible tumor doses with the lowest possible normal tissue toxicity. The need to minimize normal organ effects was recognized early in the development of RIT, and treatment-planning strategies were introduced to achieve this goal (*8–13*). This goal is analogous to the inverse planning techniques used in intensity-modulated radiotherapy for external-beam radiotherapy.

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Internal dosimetry methods for systemically administered, unsealed radiation sources continue to evolve. Treatment planning for systemic radionuclides requires assessments of radioactivity in the major organs over time to calculate the integral residence times that are needed to estimate radiation absorbed doses. Accurate measurement of the uptake and retention of the radiopharmaceuticals in organs and tissues is challenging, but a reasonably accurate assessment of radionuclide pharmacokinetics is feasible with current imaging techniques. The MIRD formalism, originally introduced as a method for estimating radiation absorbed doses from diagnostic radiopharmaceuticals, has now been widely applied in radionuclide therapy (*14*,*15*).

Recognizing the wide variation in patient sizes, the MIRD Committee developed a set of nonscalable anthropomorphic models (phantoms) for use within the schema, including a standard adult (74 kg) and a 15 y old (or representative female, 58 kg). Each model has fixed organ masses. Though the MIRD formalism provides the ability to estimate the radiation absorbed doses to patients, it does not take into account variations in whole-body and organ masses that are seen in individual patients. The use of simple geometric representations of human organs and tissues, as given in the MIRD schema, can indeed lead to either underestimation or overestimation of the true absorbed dose to organs of individual patients (*16*).

It is desirable to plan high-dose radionuclide therapy using patient-specific organ volumes. Since the radiation absorbed dose to an organ is inversely proportional to its mass, it is important to optimize the dose to the individual patient's organ to minimize systematic errors. Several adjustments to correct for differences in body and organ sizes and radionuclide kinetics have been introduced by others (*15*,*17*). Patient-specific approaches that account for variations in organ masses should enable more accurate dose estimates and, consequently, better protection against overirradiation that could lead to serious normal tissue toxicities.

Prior clinical and radiobiologic dose-escalation studies have established reasonable estimates of the maximum tolerable radiation absorbed doses to the major organs and tissues (*5*–*7*,*13*). RIT delivers relatively low initial dose rates (0.1–0.2 Gy/h to the tumor) compared with other radiotherapy modalities (4–24 Gy/h) (*18*). The radiobiology of internal emitters is therefore somewhat different than that of external-beam radiotherapy or brachytherapy. The toxicities associated with high-dose RIT extend beyond bone marrow suppression and include cardiopulmonary effects (*19*), hepatic toxicities (*20*,*21*), nephrotoxicity, and gastrointestinal tract effects.

During the last decade, we have treated >200 NHL patients using high-dose ^{131}I-labeled RIT. This report describes a simple method for adjusting radiation absorbed dose estimates using actual organ volumes. Our study involved a cohort of patients with relapsed or residual NHL who received novel high-dose myeloablative RIT with ^{131}I-tositumomab. We examined the results of this study to evaluate the benefits of CT-derived organ volumetrics and adjustments to the dose estimates compared with unadjusted assessments and standard MIRD organ models.

MATERIALS AND METHODS

We reviewed the radiation absorbed dose estimates for 84 consecutive patients with NHL who were evaluated for treatment with ^{131}I-tositumomab RIT in several ongoing phase I/II protocols at the University of Washington-affiliated medical facilities during the period between January 1990 and April 2003. Records for 84 patients were available for this analysis.

Patients

All patients entering these protocols had documented B-cell NHL in relapse after standard therapy or primary refractory disease, had evaluable disease, and were eligible to receive autologous stem-cell rescue. Only patients with tumors expressing CD20 antigen were eligible to enter the study. Entry criteria for the protocol required patients to have an Eastern Cooperative Oncology Group performance status score of >1, normal renal and liver function, and <25% cancer involvement of the bone marrow. Patients also underwent standard evaluations for stem-cell rescue eligibility, including collection of adequate number of stem cells. This trial was performed with the approval of the human subjects and radiation safety committees at the University of Washington and the Fred Hutchinson Cancer Research Center, Seattle. All patients signed informed consent and were enrolled into the study according to protocol requirements.

Radioimmunoconjugate

Radioiodination of murine monoclonal anti-CD20 antibody (tositumomab, anti-B1, immunoglobulin G2a [IgG2a]; Corixa Pharmaceuticals Inc.) was performed at the radiochemistry facility of the Division of Nuclear Medicine at the University of Washington using the chloramine-T labeling method (*6*,*8*,*9*).

Biodistribution Studies for Treatment Planning

A biodistribution study was conducted on each patient before treatment using 185–370 MBq (5–10 mCi) ^{131}I-tositumomab antibody (1.7 mg/kg) diluted to 25 mL with normal saline and infused intravenously. Anterior and posterior γ-camera images of the chest, abdomen, and pelvis were obtained after trace dose administration and then again at 48, 96, and 120 h after infusion. Measurements of whole-body activity were also obtained at the same time points. Time–activity curves for each organ were constructed from these data. Organ residence times derived from the integrated time–activity curves were used to estimate the radiation absorbed dose to organs and tissues of the body. For patients <60 y of age, the maximum normal organ dose was set at 27 Gy (2,700 rad) and for patients >60 y, the maximum normal organ dose was set at 25 Gy (2,500 rad) (*6*).

Imaging Measurements

γ-Camera images of the lungs (using ^{99m}Tc-labeled macroaggregated albumin), liver, spleen (^{99m}Tc-sulfur colloid), and kidneys (^{99m}Tc-MAG3) were obtained before the ^{131}I-trace-labeled antibody infusion to delineate these organs for quantifying the ^{131}I uptake and retention over time. Transmission images of the chest and abdomen were obtained using a 74-MBq (2 mCi) ^{131}I-filled flood source, from which we calculated the appropriate attenuation-correction factors. After infusion, serial planar (anterior and

posterior) γ-camera images of the chest, abdomen, and pelvis were obtained at approximately 0, 48, 96, and 120 h (*8*). A high-energy collimator was used with a 20% window centered on the ^{131}I γ-peak at 364 keV. A General Electric Maxxus dual-head γ-camera with a dedicated Starcam computer was used for image acquisition. Serial background-subtracted whole-body counts were obtained at the same times as the γ-camera images using a shielded detection probe with a 7.6-cm (3-in.) NaI scintillation crystal interfaced to a multichannel analyzer (model 261; Ludlum Corp.). Anterior and posterior whole-body counts were obtained with the detector directed toward the full height and width of the patient (standing as a point source, at 5-m distance). The geometric mean of the anterior and posterior whole-body counts was used to calculate whole-body retention. Whole-body counts were corrected for physical decay using an ^{131}I standard to obtain the percentage injected activity remaining at each time point.

^{99m}Tc-Derived regions of interest (ROIs) were placed over acquired ^{131}I-tositumomab images to determine the ^{131}I counts in liver, lungs, spleen, and kidneys and to generate the fractional time–activity curves for these organs. Time–activity curves were constructed for each major source organ, were fit to first- or second-order exponential functions using commercially available mathematic software (CurveExpert 1.3, Daniel Hymas; Sigma-Plot v. 4.0, Jandel Scientific), and were integrated. Residence times for lungs, liver, spleen, kidneys, bone, and total body were calculated from the individual organ retention of radioactivity obtained from ROIs drawn for these organs. Counts were corrected for background radioactivity using a region drawn in the peripheral soft tissue and were decay-corrected using an ^{131}I standard aliquot.

The amount of ^{131}I activity needed for therapy was calculated to deliver a fixed radiation absorbed dose to the critical normal organ (lungs, liver, or kidneys) receiving the highest dose.

Radiation Absorbed Dose Estimates

Standard procedures described by the MIRD Committee of the Society of Nuclear Medicine were used to estimate radiation absorbed dose to normal organs (*14*). Results were expressed in units of radiation absorbed dose per unit administered ^{131}I activity (mGy/MBq or cGy/mCi) using standard dose-assessment software (MIRDOSE2; Oak Ridge Associated Universities, Oak Ridge, TN).

Before dose calculations, we adjusted the organ residence times from the integral of the serial time–activity curves by applying the ratio (unitless) of the standard organ volume to the CT-derived volume for each major organ. The resulting adjusted residence time was then used to calculate the radiation absorbed dose (mGy/MBq) using the MIRDOSE2 software for each patient treatment plan.

Adjusting the residence time is a simplified method to account for patient-specific organ mass in the dose calculation. Briefly, for individual organs and for the whole body, this correction may be made by multiplying the calculated source-organ residence time, τ_h, by the ratio of the defined reference man or reference woman organ mass (m_{MIRD}) to the known organ mass (m_{actual}):

$$\tau_{new} \approx (\tau_h)(m_{MIRD}/m_{actual}).$$

This correction is accurate to the extent that the organ dose is mainly due to nonpenetrating radiation, such as β-particles. The new residence time for each source organ and for the remainder tissues may then be entered into MIRDOSE to estimate normal organ and whole-body doses per unit administered activity.

Statistical Analysis

The common approach to dose assessment is to ignore patient organ masses and use MIRD models. Differences between use of MIRD and patient-specific organ masses (with and without adjustment for the actual organ volumes) were analyzed using a paired *t* test. Values expressing the significance of the differences between the 2 datasets were analyzed.

RESULTS

Data from 84 patients were included in this review. Patients with a median age of 46.5 y (range, 34–74 y) had either refractory disease or relapsed disease after prior chemotherapy. Organ residence times and radiation absorbed dose estimates for the patient group using patient-specific organ masses are presented in Table 1.

Statistically significant differences were observed between the residence times estimated using the actual CT-derived organ masses and those obtained from the MIRD phantom models (Table 2). These results showed that spleen residence times correlated the least ($r = 0.22$; $P = 0.0001$) because spleens vary in size the most among the patient population. The liver residence times showed a better correlation ($r = 0.64$; $P = 0.004$) due to the smaller variability in organ size. We found the best correlation for the whole-body dose residence times ($r = 0.78$; $P = 0.0001$).

In a similar way, statistically significant differences were found for the radiation absorbed doses calculated from

TABLE 1
Dosimetry Estimate Results of Biodistribution Studies After Trace Dose of ^{131}I-Tositumomab Using MIRD Method ($n = 84$)

Organ	Mean residence time* (h)	Mean absorbed dose* (mGy/MBq)	Mean CT volume* (mL)
Lungs	9.03 (4.5–13.6)	1.67 (0.81–4.32)	1,371 (528–5,810)
Liver	12.4 (5.8–21.9)	1.03 (0.57–1.67)	1,782 (662–3,420)
Spleen	2.17 (1.38–4.89)	1.08 (0.19–1.97)	316 (50–639)
Kidneys	1.7 (0.81–3.88)	2.67 (0.32–4.40)	381 (230–661)
Whole-body mass	62.4 (30.4–87.8)	0.30 (0.16–0.38)	82.85 (57–134)†

*Range is in parentheses.
†Kilograms.

TABLE 2
Residence Times in Major Source Organs Estimated from Biodistribution Studies: MIRD Volume Versus Adjusted for Actual Volume ($n = 84$)

Organ	MIRD model mean residence time* (h)	Actual volume mean residence time* (h)	*r*	*P* value
Lungs	11.7 (1.3–22.9)	9.4 (4.3–16.6)	0.49	0.0001
Liver	11.7 (4.7–17.6)	12.5 (5.8–21.9)	0.64	0.004
Kidneys	2.2 (0.8–4.1)	1.9 (0.8–8.2)	0.45	0.0004
Spleen	3.4 (0.3–6.2)	2.2 (0.3–5)	0.22	0.0001
Whole body	78.5 (40–107.7)	70.1 (30.4–114)	0.78	0.0001

* Range is in parentheses.

model organ sizes or adjusted to account for patient-specific organ mass (Table 3). Patients received a mean administered activity of 19.4 GBq (525 mCi), ranging from 9.63 to 42.7 GBq (260–1,154 mCi) ^{131}I-tositumomab for therapy based on the adjusted dose estimates. If treatments were to have been based on standard organ volumes provided in the MIRD model, patients would have received a mean administered activity of only 16 GBq (433 mCi), ranging from 5.7 to 26.8 GBq (154–725 mCi), a statistically significant difference ($P = 0.0001$) (Table 4).

DISCUSSION

These results showed that accounting for patient-specific organ volumes from CT imaging made significant impacts on the amounts of radiolabeled antibody needed for therapy. High-dose ^{131}I-tositumomab RIT with marrow rescue (*5,7,22*) was introduced to improve on the results of low-dose nonmyeloablative treatments and standard autologous transplants (*10,12,23,24*) in management of patients with relapsed or recurrent NHL. The wide variations in biodistribution seen in individual patients, together with the large variability in normal organ sizes, suggest the need to account for these differences in treatment planning. By so doing, we believe that dose estimates are more accurate and that the amounts of ^{131}I-antibody administered will be less likely to undertreat tumors or exceed normal organ toxicity.

Internal dose assessment using patient-specific factors appears to be a useful approach in RIT, just as computerized dose assessment has been the mainstay of external-beam treatment planning. Similar concepts of treatment planning have been used with other RIT regimes (*10,24,25*). In our trials, we developed patient-specific estimation of absorbed doses to normal organs to improve the overall accuracy of treatment planning. Our treatment protocols required treatment at targeted dose levels. Other investigators have also recognized the importance of patient-specific absorbed dose assessment before high-dose RIT (*5,9,26*).

MIRDOSE2 has been used by this institution since 1989 to maintain consistency in the way radiation doses are calculated for lymphoma and leukemia patients.

Other strategies have been used to determine treatment levels. Strategies based on body weight or surface area, as with administration of cytotoxic chemotherapy, can result in inadequate treatment of tumor or overtreatment of sensitive normal tissues when doses are escalated. Radioactivity and cytotoxic chemotherapy do not have similar behavior in the normal, nontarget organs and tissues. Though many chemotherapeutic drugs need to be activated in the body before they are cytotoxic (such as cyclophosphamide) and their toxicity is organ specific, the blood-pool radioactivity in an organ during RIT can result in delivery of a significant radiation absorbed dose.

Whole-body measurements of retained radiolabeled antibody are used by others to calculate treatment dose (*11*). The whole-body measurement approach assumes (a) uniform biodistribution of the radiotracer in all organs and tissues, (b) identical residence times for the whole body and critical organs, and (c) all tissues exhibit essentially equivalent radiosensitivity. The present study, together with earlier reports from our group and those from others, have shown wide variations in individual biodistributions of radiolabeled antibody among patients with NHL. Our data also show large variations in patient size and organ mass. We believe that these differences prove the need for patient-specific dosimetry and treatment planning, particularly when high-dose, curative therapy is administered (*5,7,9–11,13,25*).

TABLE 3
Radiation Absorbed Dose to Organs Estimated from Biodistribution Studies: MIRD Volume Versus Actual Volume

Organ	MIRD model radiation absorbed dose* (mGy/MBq)	Actual volume radiation absorbed dose* (mGy/MBq)	*r*	*P* value
Lungs	1.67 (0.81–4.32)	1.30 (0.19–2.56)	0.71	0.0001
Liver	1.03 (0.57–1.67)	0.92 (0.24–2.22)	0.72	0.01
Kidneys	1.08 (0.19–1.97)	0.76 (0.18–4.81)	0.81	0.0001
Spleen	2.67 (0.32–4.40)	1.40 (0.081–5.18)	0.29	0.0001
Whole body	0.30 (0.16–0.38)	0.22 (0.022–0.40)	0.65	0.0001

*Range is in parentheses.

TABLE 4
Administered Amount of Radioactivity Based on Organ Volumes Provided in MIRD Model and After Adjustment to CT-Derived Actual Volumes

	Based on MIRD volume	Based on actual volume	*r*	*P* value
Administered activity* (GBq)	16.1 (5.7–26.9)	19.3 (9.6–42.7)	0.65	0.0001

*Range is in parentheses.

The relative radiosensitivity indication of the ability of cells to repair sublethal damage of normal tissues also is highly variable. Normal organ radiosensitivity limits the absorbed dose that may be safely delivered during radiation therapy. As we are better able to estimate radiation doses to healthy internal organs and tissues and the tolerable limits on radiation toxicity, we will be better able to use this information in treatment planning. Experience treating multiple myeloma with ^{166}Ho-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonic acid (a skeletal targeted radiotherapy) (*27*) and neuroendocrine cancer with ^{90}Y-octreotide (a radiolabeled peptide analog of somatostatin) (*28,29*) illustrates the challenge of normal organ toxicity (which in both cases were the kidneys, remote from the intended target tissues) in high-dose radionuclide therapy.

Actual patient weights and organ sizes vary considerably from those volumes described in the standard dosimetry models. For example, spleen sizes in adult patients have varied from about 50 to >600 g, whereas the spleen size in the standard MIRD adult phantom is 183 g. Since radiation absorbed dose to an organ is inversely proportional to the mass of the organ for which dose is calculated, an adjustment to dose estimation should be made for organ mass when actual organ volumes are known from CT imaging. In this article, we describe a convenient method for correcting for known organ mass (*15*). This simplified approach corrects the β-component (about 93% of the absorbed dose from ^{131}I) but does not correct the γ-component (<7% of the total). For most radionuclides, the β self-irradiation dose in a source organ is the greater contributor to total organ dose (usually >90% of the total). This correction is accurate for pure β-particle–emitting radionuclides, such as ^{90}Y and ^{32}P. The simplified method does not correct for γ-emitting radionuclides with very little β-particle energy imparted to tissue but should be useful for most β- and γ-emitting radionuclides (such as ^{131}I and ^{186}Re). It is practical, yet accurate, compared with alternative methods for patient-specific dose assessment that require complete recalculation of S values for each source→target combination using patient-specific organ parameters. In practice, the use of CT images to display organ size and geometry combined with planar imaging or SPECT to display activity in the major organs can be used to calculate patient-specific S values for each source→target organ combination. However, recalculation of voxel S values can be a time-intensive and computer-intensive process that is not practical for most treatment-planning obligations.

For our study, we obtained organ volumes from CT scans of patients' chest and abdomen to correct the source-organ residence times. Patient-specific residence times enable more accurate dose calculations for the major organs. The CT scan is a well-established method for estimating organ volumes (*30,31*).

CONCLUSION

Our study represents a novel treatment modality using high myeloablative doses with ^{131}I-tositumomab antibody and the largest cohort of NHL patients treated with RIT. This successful clinical RIT for NHL has resulted in improved long-term disease control without critical nonmarrow toxicity, which further underscores the importance of individual patient treatment planning. Although it is attractive to keep dosimetry simple and straightforward, where possible, the dosimetry should be patient specific and, further, specific to normal organs or tissues at greatest risk for life-threatening tissue damage. The organ sizes in these patients varied widely from standard MIRD anthropomorphic models. These differences produced significant differences between doses assuming standard masses and the individualized patient doses. As radiation absorbed dose estimation techniques for internal radiation emitters continue to evolve (*32*), preventing serious toxicities to normal vital organs is not only essential but also, perhaps, the ethical responsibility of all involved in treating cancer patients. In this process, one should not shy away from delivering maximal doses to the tumor with the intent to cure within the constraints of normal tissue tolerance. Paracelsus, the 16th century Swiss physician, once said, "All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy" (*33*).

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