

Dosimetric Considerations in Radioimmunotherapy and Systemic Radionuclide Therapies: A Review

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Abstract

Radiopharmaceutical therapy, once touted as the “magic bullet” in radiation oncology, is increasingly being used in the treatment of a variety of malignancies; albeit in later disease stages. With ever-increasing public and medical awareness of radiation effects, radiation dosimetry is becoming more important. Dosimetry allows administration of the maximum tolerated radiation dose to the tumor/organ to be treated but limiting radiation to critical organs. Traditional tumor dosimetry involved acquiring pretherapy planar scans and plasma estimates with a diagnostic dose of intended radiopharmaceuticals. New advancements in single photon emission computed tomography and positron emission tomography systems allow semi-quantitative measurements of radiation dosimetry thus allowing treatments tailored to each individual patient.

Keywords: Radionuclide therapy, radioimmunotherapy, quality of life

Introduction

Radiopharmaceuticals have been in use in nuclear medicine for a variety of mostly diagnostic and more recently, therapeutic procedures. Recent growing interest in the use of radionuclide therapies has been fueled by advancements and discovery of targeted molecular therapies. Targeted radionuclide therapy (increasingly referred to as molecular radiotherapy) is somewhat similar to external beam therapy in that cancer cell destruction is achieved by means of radiation-induced damage to cellular DNA. In essence, targeted radionuclide therapies have the exquisite specificity of molecule-specific cellular recognition combined with the antineoplastic effects of ionizing radiation. Being a systemic treatment, its cross-fire effect can additionally destroy adjacent tumor cells even if they lack the specific tumor-associated receptor and has the potential to simultaneously eliminate both

the primary tumor site and cancer that has spread throughout the body.

Molecular radiotherapy consists of a targeting vehicle, which binds to receptor, and a radionuclide with properties that be tailored with the clinical therapeutic application. Three types of particulate radiation that can be used are β -particles, α -particles, and Auger electrons, which can irradiate tissue volumes with multicellular, cellular, and subcellular dimensions, respectively. Combining this with decay characteristics, tissue ranges, and chemistries of the differing radionuclides offers the possibility of personalizing therapy to the needs of an individual patient.

Internal tumor radiation dose estimates are not routinely used in therapy planning of individual patients in targeted internal emitter therapy, in the way that dose information is used in external beam radiation dose treatment planning. The amount of radioactivity is usually given to most patients adjusted for total body weight or external surface area. A carefully planned tumor radiation dose is not developed for each patient to optimize therapy. An exception is the treatment of B-cell lymphoma with anti-CD20 antibodies labeled to ¹³¹I (tositumomab

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Bexxar®) where therapy is based on whole body (WB) radiation absorbed dose.

The principles of tumor dosimetry for planning therapy with internally administered radiopharmaceuticals are similar to those for external-beam radiation therapy (EBRT). Additionally, maximum absorbed radiation doses to critical organs are referenced largely from experience with EBRT. Dosimetry enables the conversion of the total number of radionuclide transformations in a particular source tissue to absorbed dose in a target tissue. Such conversion requires information on emission properties of the radionuclide as well as source-target tissue anatomy and composition.

Monitoring toxicity generally allows the treating physician to reduce subsequent doses for radiopharmaceuticals given repeatedly; however, underdosing, which may result in lower efficacy remains an important concern especially since variations in radiation absorbed dose cannot always be accounted for by adjusting for body surface area or mass. Thus, one of the aims of tumor dosimetry in any radiation therapy (EBRT or radioimmunotherapy [RIT]) should be to maximize radiation dose to tumor while minimizing the irradiation of normal tissues. Patient-specific dosimetry is therefore attractive, allowing determination of the administered activity of radionuclides for each individual patient through pretherapy dosimetric studies with trace-labeled radionuclides. The other important aspect is prediction of tumor response and toxicity following radionuclide dose administration, essential to the implementation of any cancer therapy program.

Difference between Targeted Radionuclide Therapy and External-beam Radiation Therapy

Multiple fractions of high dose rate radiation are characteristic of EBRT and the benefit from such dose fractionation is well established. Average radiation dose rates involved in targeted radionuclide therapies are much lower than those encountered in EBRT, or even in continuous low dose-rate brachytherapy. For example, most radioimmunotherapy (RIT) treatments will achieve average dose rates that are substantially lower than 0.5 Gy/h. Continuous and continuously decreasing low dose rate radiation characteristic of radionuclide therapies seems to destroy cells primarily through apoptosis, rather than through necrosis characteristic of the cellular effects of EBRT and chemotherapy. Additionally, significant absorbed radiation doses may be received by radiosensitive organs, particularly the active bone marrow, lungs, and organs due to radionuclide biodistribution. Patient-specific calculation

of radiation doses delivered to tumors and normal tissues are routine in EBRT, and calibration of linear accelerators along with phantom and *in vivo* dosimetry optimize accuracy of external beam dose delivery. Radiation dosimetry for radionuclide therapies has not yet reached the sophistication of radiation dosimetry for external beam and sealed source radiotherapy, largely due to difficulties in quantification of dose distribution. In this respect, radionuclide therapy is unique because the radiolabeled drug pharmacokinetics and radiation dose distribution can be estimated for an individual patient using a nontherapeutic amount of the radiolabeled drug intended for subsequent therapy. If the biodistribution are the same for diagnostic and therapy doses of radionuclide, diagnostic studies can be very useful to predict subsequent radiation doses from therapy. External planar imaging with a gamma camera has traditionally been used to measure radioactivity. Single photon emission computed tomography (SPECT) and positron emission tomography (PET), especially when combined with computed tomography represent newer and attractive, but less established, methods for quantifying pharmacokinetics. The pharmacokinetics and radiation dosimetry of different radiolabeled compounds may be compared to evaluate their relative advantages. A complex relationship exists in tumor dosimetry because radionuclides do not reside in only one organ and as such calculation of absorbed dose to particular organs must take into account all possible source organs. Particulate emissions, such as α - or β -particles are generally absorbed within the tissue of origin. Photons, on the other hand, depending on their energy, will deposit energy in both the source tissue and other adjacent and nonadjacent tissues.

In this review, we will show how patient dosimetry is used in the dose determination of specific targeted radionuclide therapies. Recent advancements in both scientific and scintigraphic methods are changing how we calculate patient-specific dosimetry accurately. It is not the aim of this review to delve into the specific physics and complicated formulas used in dosimetric calculations; however, certain basic terms used in patient dosimetry may need to be introduced here.

Glossary of Terms

Absorbed dose expressed in S.I unit of gray ("rads" in older texts referring to radiation absorbed dose) is defined as the energy that is absorbed in a unit measure of tissue mass.

Dose-volume histogram is a graphical representation of the fraction of the tumor or organ volume receiving a specified radiation dose versus the administered dose. This presents the minimum, mean and maximum

doses and the dispersion about the mean dose with a more nonuniform dose distribution having a greater dispersion. An obvious advantage is the ability to fuse and register tomographic images from different modalities with the 3-dimensional activity distributions measured by scintigraphic imaging, thus allowing correlation of the radiation doses with tumor and normal organs.^[1]

Equivalent dose is based on the average absorbed radiation doses in a tissue or organ weighted by the radiation weighting factor for that radiation actually impinging on a tissue or organ. The unit of equivalent dose has an SI unit of sievert and conventional unit of rem (rad equivalent in man or mammal).

Maximum tolerated dose (MTD) refers to the highest dose of a treatment that will produce the desired effect without unacceptable toxicity or side effects.

Source organ is the organ whereby the radionuclide in question may reside.

Target organ is the organ of interest receiving absorbed radiation during dosimetric calculation.

S factor is the absorbed dose to a target region per unit cumulated activity in the sources. The total absorbed dose to a target region is then the sum of dose contributions to the target from all different source regions.

Medical Internal Radiation Dose Schema

This methodology, developed by the Medical Internal Radiation Dose (MIRD) committee of the Society of Nuclear Medicine,^[2] which is widely used for internal radiation dose calculations in medicine, includes age- and sex-specific reference data for human anatomy and body composition. One observation made from previous studies was that the absorbed fractions required to obtain S values were calculated by generating an idealized model of human anatomy defined as a collection of appropriately placed distinct organ volumes with mass and composition that were selected to reflect standard human anatomy (ie, standard man) and this was later extended to include female and pediatric models.^[3] Application of the resulting S values, therefore, to patient anatomies that deviate substantially from the idealized model will lead to errors. Furthermore, use of a standard model precluded the tabulation of S values for tumors, because tumors do not come in standard dimensions or positions. In a typical clinical scenario, direct blood taking or scintigraphic images obtained at different time points after injection of the radiopharmaceutical are used

to estimate the concentration of radioactivity in a specific region of interest (blood, kidneys, WB, and others). The level of activity obtained at different times after injection when plotted against time in a graphical method gives a time-activity curve for a particular organ. The integral of this curve gives the total number of disintegrations or the cumulated activity for the region. Age- and sex-specific habitus other than the original 70 kg adult anthropomorphic model, known as the standard man, have been incorporated into the MIRD schema following research by Christy and Eckerman.^[3]

In the patient-specific treatment planning paradigm, using these kinetic data, the corresponding cumulated activity and residence times as well as the absorbed radiation doses per unit administered activity can be calculated. The actual therapeutic administered activity is the activity projected to deliver MTDs to one or more critical tissues or less commonly, a minimum effective dose to the tumor or other target tissue. In the case of targeted radiopharmaceutical therapies where the uptake of the radiopharmaceutical is saturable, or nonlinear, mathematic modeling, for example, compartmental, of the tracer kinetic data may be useful in determining the optimum dose and activity of the therapeutic radiopharmaceuticals. After the therapeutic administration, serial time-activity measurements, cumulated activity, and absorbed dose calculations maybe repeated and the projected as well as actual therapeutic absorbed doses can be compared. Several techniques have been developed to improve the accuracy of radiation dose estimates beyond the traditional MIRD scheme. These include techniques for patient- and position-specific radiation dosimetry. Spatial nonuniformity of administered radionuclide dose has also become increasingly important at the macro- and microscopic levels. Nonuniformity of radiation dose in target tissues, such as tumor ,makes it difficult to accurately predict therapeutic response in radionuclide therapy. Three approaches have been used to allow calculation of macroscopic nonuniform dose distributions, including dose point kernel convolution; Monte-Carlo simulation and voxel S factors. Corresponding dose-volume histograms can be derived once a dose distribution has been calculated via one of these 3 methods. To be optimal, such dosimetric estimations require time-consuming and sophisticated methods, including pharmacokinetic, biodistribution, and washout studies using the pharmaceutical and the radionuclide to be used for therapy. This may be impossible for practical reasons related to the patient's status and for physical reasons. In therapeutic nuclear medicine the absorbed dose to tumors is important in evaluating treatment efficacy. Accurate estimation of the absorbed dose to normal organs is important in assessing likely toxicity. The rate at which the

absorbed dose is delivered, the manner by which it is delivered (α -particles, β -particles, or Auger electrons), the radiobiologic characteristics of the tumor tissue or normal organ, and the specific treatment history of the patient receiving radionuclide therapy all affect response to a specific total absorbed dose.^[4] The dosimetric requirements of therapeutic nuclear medicine have led to ongoing interest and improvements in radionuclide dosimetry. To support the calculation of nonuniform absorbed doses and to account for nonuniform activity distributions at the level of imaging instrumentation voxels, the MIRDO-15 Committee has also published S value tabulations for different voxel sizes and source-target voxel distances.^[5,6] Because use of previously tabulated S values requires a fixed anatomic model, this approach is not easily amenable to geometries that deviate substantially from the fixed anatomic models. Voxel S values overcome this problem and have been adopted in several dose calculation programs.^[7] Currently for most dosimetric uses, Organ Level Internal Dose Assessment (OLINDA) is a US Food and Drug Administration (FDA) approved device that includes S values specific to 10 phantoms and 5 organ models for more than 800 radionuclides, including α -particle emitters. The program also includes a pharmacokinetic module that may be used to determine organ cumulated activities. Recent advances including the increase in computer processing power and the availability of 3D imaging methodologies, particularly with SPECT/CT and PET/CT, have increased interest for direct image-based dosimetry techniques. The essential requirements for 3D imaging-based dosimetry are the availability of 3D anatomic imaging studies (CT or MRI); at least one 3D imaging study of the radioactivity distribution (PET or SPECT) and software that implements a point-kernel or Monte Carlo calculation methodology to estimate the spatial distribution of absorbed dose. The 3D-ID software package is one example that takes the distribution of radiolabelled antibody for a given patient (from SPECT or PET) and combines it with anatomic information (from CT or MRI) to yield absorbed dose estimates that are specific to a particular patient's biodistribution and anatomy.^[8]

Red Marrow Dosimetry

Absorbed doses as low as 3 Gy to the red marrow induce 1% of leukemia within 10 years after exposure, and the probability of survival decreases rapidly beyond 4 Gy to reach an LD50 (death of 50% of individuals) between 5 and 6 Gy.^[9] This implies that the red marrow maximal tolerated dose will be reached for a specific uptake much lower than the uptake in other organs. A hurdle in estimating the red marrow absorbed dose is its nonhomogeneous nature, with a complex mixture of trabecular bone, cortical bone, active red marrow, and

inactive marrow. Improvements to the MIRDO model were proposed to take this microstructure into account in S factor computation. In majority of nonmyeloablative radionuclide therapy, the red marrow toxicity has been determined to be the dose-limiting organ. As a result, red marrow has received the greatest attention in terms of developing and examining dosimetry methodologies. The dosimetry approaches can be divided into blood- or imaging-based methods, depending on whether or not the radiopharmaceutical specifically localizes to blood, bone, or marrow components, including tumor metastases in the marrow. The red marrow is a complex organ representing challenges both in terms of estimating activity concentration kinetics for cumulated activity determination and also for Monte Carlo calculation of absorbed fractions. In estimating the cumulated activity, progress has been made toward adopting a standardized, blood-based approach, and several red marrow dose-response studies have been reported. One such study found that absorbed dose to the red marrow or total body predicted hematologic toxicity better than administered activity or administered activity per meter squared. The analysis and conclusions were confined to ¹³¹I-labeled antibodies and antibody fragments that did not bind to blood, bone, or marrow cellular components.^[10]

Renal Dosimetry

Radiation nephropathy following EBRT has been previously described. Acute radiation nephropathy is defined as signs of kidney failure developing within 6–12 months after irradiation while pathologic kidney changes include atrophy, tubulointerstitial scarring, mesangiolysis and thrombotic microangiopathy. Acute radiation nephropathy can be reversible or progress to chronic radiation nephropathy. In EBRT, kidney dose limits of 15–17 Gy in 2 Gy fractions are considered safe.^[11] Doses of 23 Gy cause chronic kidney failure in approximately 5% of patients within 5 years.^[12]

The incidence of renal pathology has been highly dependent on the radionuclide used. ¹¹¹In, an Auger-emitter, with particle ranges that are less than a cell diameter, has shown minimal toxicity at estimated kidney absorbed doses of 45 Gy (cumulative administered activities of 58 GBq/m²), whereas ⁹⁰Y, with long range emissions of up to 12 mm in tissue, has led to renal toxicity at administered activities up to 1.9 GBq/m².^[13] In many peptide receptor radionuclide therapy (PRRT) clinical trials, individual dosimetric calculations and renal protection using amino acid infusions have been performed to avoid excessive renal radiation doses.

The megalin-cubilin complex is a receptor involved in renal reabsorption of ligands, such as (binding) proteins, hormones, drugs, toxins, and enzymes. Studies have shown

that majority of radiolabeled analogs are excreted in the urine, mostly as the intact analog. Due to partial reabsorption of radiolabeled peptides after glomerular filtration, the retention of radioactivity in the radiosensitive kidney is substantial with most radioactivity retained in the proximal tubules in the renal cortex, while less uptake was found in the outer medulla with no radioactivity found in cortical glomeruli, distal tubules, inner medulla, or renal pelvis.

Infusion of cationic amino acids, lysine and arginine, has been shown to block renal tubular peptide reabsorption in general and is widely used in patients undergoing PRRT. As a result, renal uptake of radiolabeled peptides is significantly reduced in patients receiving amino acids compared with controls. This allows the administration of higher activities during therapy to increase the therapeutic effect of the radiopharmaceuticals.

Dosimetry and Bone Pain Palliation

Bone-seeking radiopharmaceuticals used for bone pain palliation are preferred for widespread painful bone metastasis.^[14,15] Since multiple sites of osseous metastases are common and some patients have multifocal bone pain, systemic targeted treatment of the skeletal metastatic sites offers the potential of pain relief with minimal side effects. Radiopharmaceuticals that have been developed for the treatment of painful bone metastases use the following radionuclides ³²P, ⁸⁹Sr, ^{117m}Sn, ¹⁵³Sm, ¹⁷⁷Lu, ¹⁸⁶Re, and ¹⁸⁸Re. The more commonly used agents being Strontium and Samarium. The sources of radiation within bone differ with the radiopharmaceutical used: The metallic chelated radiotracers tend to chemically absorb to the trabecular surface, whereas ³²P and ⁸⁹Sr (as the chloride) distribute more widely throughout bone. Due to the heterogeneity of radiopharmaceutical uptake, specula thickening, tumor and marrow distribution, there is variation in dosimetry.^{[14]89} Sr is an element and behaves biologically similar to calcium. It localizes in bone primarily in areas of osteoblastic activity. ⁸⁹Sr has a physical half-life of 50.5 days and emits a β -particle with a maximum energy of 1.46 MeV and an average soft tissue range of 2.4 mm. The usual therapeutic dose is 148 MBq (4 mCi). After intravenous administration, ⁸⁹Sr is concentrated in bone in proportion to osteoblastic activity. Of the ⁸⁹Sr that is not concentrated in bone, about 80% is excreted through the kidneys and about 20% through the gastrointestinal system.^[16] ¹⁵³Sm is a nuclide with a physical half-life of 1.9 days and decays by β -emission. The β -particle has a mean energy of 0.23 MeV, and an average soft tissue range of 0.6 mm. The β -ray is accompanied by a 103 keV γ -ray, which is 28% abundant and allows for scintigraphic imaging. ¹⁵³Sm is complexed with ethylenediaminetetra-methylene

phosphonic acid to form ¹⁵³Sm-EDTMP. This phosphonate complex concentrates in the skeleton, in proportion to osteoblastic activity. About 65% of the dose remains in the skeleton. The urinary excretion is nearly complete by 6 h.^[17] If ¹⁵³Sm is used, the patient is weighed and a weight-dependent dose of 37 MBq/kg (1 mCi/kg) is administered.

¹³¹I-MIBG in Neuroendocrine Tumors and Neuroblastoma

Most centers using ¹³¹I Metaiodobenzylguanidine (MIBG) for therapy have had to adopt a pragmatic approach with regard to the amount of radioactivity given being limited by factors such as cost, availability of inpatient isolation rooms in hospital, and the patients' ability to tolerate the treatment. Activities of ¹³¹I-MIBG administered for treatment of patients suffering from neuroblastoma show considerable variation between centers. At some, a standard activity is given regardless of body weight.^[18] At others, dosimetric estimation studies are performed prior to therapy to calculate the activity which will result in a certain radiation absorbed dose to the WB, liver and tumor. ¹³¹I is a radioisotope with a physical half-life of 8.06 days and decays by β - and γ -emissions. The β -particle has a mean energy of 0.19 MeV, and a soft tissue penetration range of 0.6–2.0 mm. There is no consensus in the literature of any clear benefit from dosimetry as opposed to an empirical approach used for dose calculation. The use of ¹²³I-MIBG (instead of ¹³¹I) to assess WB clearance has been reported as inaccurate due to quicker clearance of ¹³¹I-MIBG, as there is increased cell damage during therapy. It has also been suggested that the increased amount of carrier found in therapeutic doses of ¹³¹I-MIBG may affect kinetics and as such differ from pharmacokinetics as predicted by ¹²³I. Monsieurs *et al* found that by applying a correction factor, it was feasible to use ¹²³I-MIBG to calculate WB doses of therapeutic ¹³¹I-MIBG.^[19] However, there are no studies comparing the outcomes of patients using dosimetric versus empirical treatment. In the dosimetric approach, an initial tracer study is carried out, usually 1–3 weeks prior to the therapy administration. The therapy activity was subsequently chosen to limit the WB to WB dose to a predetermined amount of usually 2 Gy. Two simpler methods of prescribing the therapy activity have been considered. The first uses the relationship between WB dose and the WB weight to calculate the activity necessary to deliver a 2Gy WB dose. The second uses an average WB retention curve to prescribe the activity required to deliver a 2 Gy WB dose. Fielding *et al* showed that, use of a tracer study to prescribe the final activity for therapy is the method of choice for dose prescription.^[20] The kinetics of the ¹³¹I-MIBG in each individual patient greatly affects the WB dose. Thus the

relationship between WB dose and whole body weight is too poor to enable accurate WB dose prescription from a patient's body weight. There are few reports of RIT in treating neuroblastoma. 3F8 is a murine IgG3 monoclonal antibody specific for ganglioside GD2 and reacts strongly with neuroblastoma and melanoma cell lines. In reactive neuroblastoma cell lines, >98% of the cells are antigen-positive. Yeh^[21] estimated radiation dose delivered to tumor by ¹³¹I-labeled 3F8 based on serial scintigraphic studies and assessment of tumor size by CT and MRI. These estimates were compared with tissue counts in resected tumors after antibody administration. Good agreement between the measured tissue radioactivity and the estimates based on planar scintigraphy validate dosimetry calculations. The estimated radioactivity and the calculated radiation dose showed that 36 cGy/mCi was delivered to neuroblastoma and 3–5 cGy/mCi to blood. Delivery of 4000 cGy to the tumor is possible and normal tissue receiving less than 400 cGy, except for the blood, which is exposed to a significantly higher dose.

Cheung^[22] subsequently went on to treat 9 patients with refractory neuroblastoma with escalating doses of ¹³¹I-labeled 3F8 (6–12 mCi/kg). In his analysis, dosimetry of marrow ranged from 0.36–2.2 cGy/mCi depending on body size and the average tumor dose was 20–36 cGy/mCi.

In a single case report, Larson *et al* demonstrated the use of ¹²⁴I-labeled 3F8 antibody in dosimetric calculations using PET/CT.^[23] Activity concentration was plotted against time for documented abdominal and vertebral tumors. Exponential fits were used to determine initial uptake, clearance time, and cumulated concentration with radiation dose determined using the MIRD schema. Radiation absorbed dose to tumor sites of maximum uptake for a therapeutic administration of ¹³¹I-labeled 3F8 was estimated to be 7.55 rad/mCi. Dose from the remainder of the body was estimated to be no more than 0.4 rad/mCi. However, it should be noted that ¹²⁴I has a complex decay scheme with many high-energy gamma rays and a positron abundance of only 25%.

Radioimmunotherapy of Lymphoma

Pretreatment dosimetry plays an important role in many RIT applications. It is particularly important in early trials to determine the biodistribution of the radiopharmaceutical, confirm tumor uptake, establish a database of estimated normal organ doses, to estimate absorbed radiation doses to red marrow, and to ensure that the delivered doses remain within a safe range. The methodology used to calculate activity and residence times for the WB, lungs, liver, spleen, and kidney has been previously described by Wiseman *et al*.^[24,25] Bone marrow is commonly the dose-limiting organ for

nonmyeloablative RIT while the lung is the limiting organ in myeloablative RIT. In the myeloablative setting, dosimetry provides a basis for determining dose-limiting critical organ toxicity. Dosimetry also provides a means of individualized patient dosing, which is important for agents that exhibit significant variability in biodistribution or urinary excretion, such as ¹³¹I.^[25,26] Bexxar and Zevalin are 2 radiolabelled anti-CD20 antibodies that are available for treatment of follicular low-grade non-Hodgkin's lymphoma (NHL). Bexxar contains ¹³¹I-labeled tositumomab, and Zevalin contains ⁹⁰Y-labeled ibritumomab. In both cases an unlabeled antibody, rituximab, is infused before the radiolabeled component is administered. Because the interaction of anti-CD20 antibodies and the CD20 epitope does not result in internalization of the bound antibody, ¹³¹I labeled anti-CD20 antibody can be used for the treatment of B-cell lymphomas. Radiometals such as ⁹⁰Y and ¹¹¹In become insoluble moieties if the bond to the antibody is lysed by plasma or cytoplasmic proteolytic enzymes. The radiotherapeutic component of Zevalin is ⁹⁰Y that is linked with tiuxetan to the murine monoclonal antibody ibritumomab. With the metal binding moiety tiuxetan, the entire molecule is either ¹¹¹In or ⁹⁰Y ibritumomab tiuxetan. Consideration of the radiation dose to bone marrow is an important concern when determining the therapeutic dose of RIT. Bone marrow dosimetry requires repeated blood sampling over time, and the dose to bone marrow will vary depending on the amount of tumor involvement in bone marrow.

Bexxar

Nonmyeloablative use

Studies with ¹³¹I tositumomab for the treatment of NHL have shown that a 10- to 15-fold higher dose of radiation energy can be delivered to the tumors compared with WB.^[27] Initial dosimetric studies confirmed that there is up to a 5-fold variation in the clearance rate of the antibody. Therefore, because the antibody clearance rates are variable, the administered therapeutic activity required to deliver identical WB radiation doses to individual patients is variable. Factors affecting clearance of the antibody include the size of the patient's tumors (bulky versus microscopic disease), splenomegaly, lean body mass, and the amount of bone marrow involvement in the disease. Individuals with a rapid clearance rate require a higher dose of radiation to deliver the total body MTD compared with individuals with a slow clearance rate. Clinical trials at the University of Michigan determined that hematologic toxicity as well as a dose and clinical response relationship existed based on the WB radiation absorbed dose rather than on an mCi/kg dosing schedule.^[28] The MTD of ¹³¹I tositumomab (65 cGy for patients with 100,000–150,000 platelets/mm³ and 75 cGy for patients with >150,000 platelets/mm³)

was determined in phase I dose escalation studies. For patients who have undergone autologous stem cell transplantation, the MTD is 45 cGy.^[29] The total-body MTD of 75 cGy defined by dosimetry studies was determined during a phase I dose-escalation study in which the total-body doses were 25–85 cGy. Two of three patients given WB doses of 85 cGy experienced grade 3 and 4 leukopenia and thrombocytopenia. Therefore, the MTD was determined to be 75 cGy for patients who had not undergone autologous bone marrow transplantation.^[30] By these calculations, the administered dose to deliver a 75 cGy total-body dose of ¹³¹I to 634 NHL patients undergoing ¹³¹I tositumomab therapy varied from 43 to 275 mCi.^[31] In tositumomab and ¹³¹I tositumomab dose escalation studies, the radiation dose was administered to patients, defined by dosimetry, correlated with toxicity, and allowed for the determination of the MTD. For the present, WB dosimetry is routinely applied for RIT with tositumomab and ¹³¹I tositumomab and has proven to be a reliable method to determine the patient-specific maximally tolerated therapeutic radiation dose to maximize efficacy while minimizing organ and bone marrow toxicity.

Myeloablative use

Myeloablative conditioning traditionally comprises high-dose chemotherapy with or without total body irradiation but is associated with toxicity, which limits its use in certain patient groups, such as the elderly. Press *et al*, investigated the possibility of replacing external beam total-body irradiation with targeted RIT for patients with relapsed leukemia and lymphomas undergoing bone marrow or stem cell transplantation. Since total-body irradiation with EBRT delivers as much radiation to normal organs as it does to tumor cells, the idea that selective delivery of radiotherapy to tumor sites with radiolabelled antibodies should be a superior approach, capable of delivering more radiation to tumor cells and less to normal organs. The main aim of the study was to determine the MTD of ¹³¹I-labeled antibody in the setting of autologous bone marrow support.

Test infusions of antibodies trace labeled with ¹³¹I (5–10 mCi) were administered followed by serial quantitative gamma camera imaging. Data obtained from gamma camera imaging and from absolute quantification of radioactivity in tumor biopsies by gamma counting were used to estimate absorbed radiation doses for each assessable tumor site and for critical normal organs, including the liver, lungs, and kidneys.

In order to compare the biodistribution of different antibodies, patients received infusions of two or three different trace-labeled antibodies. Those patients having met favorable biodistribution criteria went on to

receive an infusion of a therapeutic dose of a ¹³¹I-labeled antibody; either MB1 (anti-CD37), 1F5 (anti-CD20), B1 (anti-CD20), or anti-idiotypic at the dose (0.5, 2.5, or 10 mg/kg) found to be most advantageous for that particular patient.

Dose escalation was performed according to the projected dose of radiation absorbed by the critical organ receiving the greatest radiation exposure. Three patient cohorts were treated in a phase I trial with doses of ¹³¹I-labeled antibody calculated to deliver 10, 15, 17, 20, 24, 27, and 31 Gy to the normal organ receiving the highest level of radiation (200–800 mCi was administered).

Early studies showed patients were more likely to have favorable biodistribution with anti-CD20 antibodies than with anti-CD37 or anti-idiotypic antibodies.^[32] Toxicities were minimal at the first five dose levels tested (delivering 10–24 Gy to normal organs). In contrast, patients treated at the two highest dose levels (delivering 27–31 Gy to normal organs) experienced non-hematological toxicities such as asthenia and vomiting.

Myelosuppression was universally observed following high-dose RIT and cardiopulmonary toxicity was the primary dose-limiting, nonhematologic toxicity. MTD levels were determined to be 560–777 mCi ¹³¹I delivering average 27 Gy to normal organs. Subsequent phase II study of high-dose ¹³¹I-tositumomab therapy in 25 patients with relapsed B-cell NHL, 21 patients with a favorable biodistribution were treated with 345–78 mCi of ¹³¹I-tositumomab, which delivered 25–31 Gy to dose-limiting normal organs and higher doses (27–92 Gy) to tumor sites.^[33]

A conditioning phase I/II study by Press *et al* combining ¹³¹I-tositumomab with high-dose etoposide/cyclophosphamide and stem-cell transplantation was conducted to define the MTD of each component of this regimen.^[34] MTDs were determined to be 25 Gy (1.7 mg/kg of ¹³¹I tositumomab), 60 mg/kg etoposide, and 100 mg/kg cyclophosphamide. Interestingly, this was statistically superior to the 2-year overall and progression-free survival rates of a nonrandomized control group of patients treated at the same institution with the same doses of etoposide and cyclophosphamide, plus total body irradiation rather than ¹³¹I-tositumomab.

Zevalin

Nonmyeloablative use

The murine immunoglobulin IgG1 kappa anti-CD20 monoclonal antibody (ibrutumomab) conjugated to the linker-chelator tiuxetan has the capability of securely chelating ¹¹¹In for imaging and dosimetry as well as ⁹⁰Y for therapy. The physical half-life of

^{111}In (2.8 days) is similar to that of ^{90}Y (2.7 days). The biodistribution profile of ^{111}In -labeled Zevalin is sufficiently comparable and thought to predict that of the ^{90}Y -labeled antibody. The tiuxetan linker–chelator provides a high-affinity, conformationally restricted chelation site. This chelator provides stability *in vivo* between the ^{90}Y radiometal and ibritumomab, and coupled with a predictable pharmacokinetic profile, allows weight-based dosing with no requirement for determination of WB clearance.^[35] Preclinical studies have demonstrated that biodistribution of the ^{90}Y -labeled antibody is reliably predicted by the ^{111}In -labeled antibody.^[36,37] Initial estimates of absorbed radiation dose were made at the clinical sites using quantitative imaging and blood sampling data with the MIRDOSE3 software program.^[38] Following the injection of ^{111}In -Zevalin, WB scans were performed and blood samples were drawn for dosimetry calculations. Anterior and posterior images were taken. The subsequent process involves estimating region of interest ^{111}In activity content versus time based on geometric mean counts and a WB–averaged attenuation correction factor derived from the first WB count (ie, before the patient has exerted any activity) followed by performing necessary decay corrections to convert ^{111}In activity to ^{90}Y activity. By estimating the residence time as the area under the activity versus time curve using exponential curve fitting and estimating dose from residence time using the MIRDOSE3 computer program. The central dosimetry used patient-specific organ masses for spleen and liver, estimated from organ volume determined by CT. Residence times in red marrow were derived from blood time–activity curves following the method of Sgouros.^[32] Values were obtained for red marrow mass by matching the patient’s weight with an appropriate phantom in MIRDOSE3. The organ doses are assigned to either of two categories. The first category includes the specific organs for which the absorbed radiation dose is estimated from residence times specifically determined for these regions of interests (ROIs) by imaging or blood sampling. Since ^{90}Y is a pure beta-emitter, virtually all the dose to each of these organs is due to ^{90}Y transformations occurring within the target organ (ie, by self-irradiation). An exception is the calculation of bone marrow dose, which, because of the physical distribution of this tissue, must account for beta energy deposition from ^{90}Y on adjacent bone surfaces. The second category comprises other target organs. The absorbed radiation dose to other organs is estimated from the total-body remainder residence time. This method, as incorporated into MIRDOSE3, assumes that all remaining activity is distributed among these organs in proportion to their mass. For pure beta-emitters, this assumption results in equal doses for each of the remainder organs. Median estimated absorbed radiation doses from ^{90}Y -labeled Zevalin were 8.1 Gy (range, 4.2–23.0 Gy) to

the spleen, 5.1 Gy (range, 2.6–12.0 Gy) to the liver, 2.0 Gy (range, 1.4–5.3 Gy) to the lungs, 0.22 Gy (range, 0.01–0.66 Gy) to the kidneys and 0.74 Gy (range, 0.29–1.2 Gy) to the red marrow. In rituximab refractory patients, the spleen received the highest absorbed radiation dose followed by the liver. The absorbed radiation dose estimates to the liver remained well within a safe range, and no hepatic dysfunction or toxicity was detected. Patients with higher baseline serum rituximab levels (from prior rituximab immunotherapy) had significantly higher pulmonary dose estimates, but all lung doses were well below lung tolerance and no lung toxicity was noted. The pattern of normal organ doses is similar to results reported in other studies of RIT. The median or mean dose was 22–36 cGy/mCi to the spleen and 13–23 cGy/mCi to the liver.^[39] The only toxicity of note in this trial was transient and reversible hematologic suppression, which did not correlate with estimated absorbed radiation dose to red marrow or the total body. One possible explanation for the lack of correlation is that the blood-based method of bone marrow dosimetry used here does not account for targeting of the radiopharmaceutical to NHL within the marrow. The value of radiation dosimetry is restricted if the radiation absorbed dose to the dose-limiting organ does not correlate with toxicity. Results from studies of the Zevalin regimen indicate that radiation absorbed dose does not exceed safe limits and does not correlate with hematologic toxicity. Since absorbed dose versus toxicity studies did not show a correlation of absorbed dose with toxicity, this agent is now prescribed on a per-bodyweight basis. Therefore, dosimetry has been eliminated from the Zevalin regimen. While imaging using ^{111}In -labeled Zevalin is no longer a necessity for dosimetry, it is still performed to assess whether biodistribution is acceptable prior to proceeding with an injection of the ^{90}Y -labeled Zevalin therapeutic dose. The therapeutic dose of ^{90}Y -labeled Zevalin was determined in Phase I and Phase II clinical trials. Patients received ^{90}Y -labeled Zevalin at fixed single doses of 10–50 mCi in a dose-escalation trial, with 3 patients receiving multiple doses leading to a cumulative exposure of 70 mCi. The nonmyeloablative MTD of ^{90}Y -labeled Zevalin was identified as 0.4 mCi/kg up to a maximum of 32 mCi for patients with baseline platelet counts $>150,000$ plt/ mm^3 . Patients with baseline thrombocytopenia were not dose-escalated beyond 0.3 mCi/kg.

Myeloablative use

In autologous stem cell transplantation

A standard dose of ^{90}Y -ibritumomab tiuxetan plus chemotherapy in autologous stem cell transplantation have been investigated by several authors and concluded that compared with total body irradiation, this is a well-tolerated and effective regimen for older patients with poor-risk NHL undergoing autologous stem cell

transplantation (SCT). More importantly, studies on high-dose and escalated-dose ^{90}Y -ibritumomab tiuxetan plus chemotherapy for autologous SCT conducted by Nademanee *et al*^[40] (median administered dose 71.6 mCi and dosimetric analyses to deliver a target dose of 1000 cGy to normal organs) as well as Winters *et al* (escalating dose 0.3–1.2 mCi/kg plus high-dose BEAM and patient-specific doses of Zevalin calculated to deliver escalating radiation doses of 300–2100 cGy to critical organs were administered) demonstrated a tolerable toxicity profile with rapid engraftment.

High-dose and escalated-dose ^{90}Y -ibritumomab tiuxetan as monotherapy in conditioning regimen with tandem SCT was investigated by Devizzi *et al*.^[41] Zevalin was administered at doses of 0.8 or 1.2 mCi/kg. Toxicity was as expected, but absence was noted of the frequent severe complications seen with conventional high-dose chemotherapy. Vanazzi *et al*^[42] showed in a study with refractory or chemo-resistant NHL patients that following dosimetry, 0.8, 1.2, or 1.5 mCi/kg ^{90}Y ibritumomab tiuxetan showed acceptable radiation absorbed doses to critical normal organs in all cases and expected hematologic toxicity. Thus the authors suggested in heavily pretreated patients, an activity of 1.5 mCi/kg is suitable for those patients with normal platelet counts and a reduced dose of 1.2 mCi/kg for patients with a platelet count of 150×10^9 .

In allogenic stem cell transplantation

Fietz *et al*^[43] reported results with two relapsed lymphoma patients post-allogenic SCT with a conditioning regimen consisting of rituximab, ^{90}Y ibritumomab tiuxetan 0.4 mCi/kg, fludarabine, and cyclophosphamide.

Radioimmunotherapy of Solid Organ Tumors

Malignant glioma/recurrent glioblastoma

α -Emitter RIT is generally pursued in settings where rapid exposure of the tumor to the labeled monoclonal antibody can be achieved. By focusing on malignancies with limited tumor depth, the short range of α -particles can be advantageous.

Zalutsky *et al*^[44] investigated the use of ^{211}At -labeled chimeric 81C6 antitenascin monoclonal antibodies administered to surgically created (tumor) resection cavities in patients with recurrent malignant gliomas. LD10 for intravenously administered ^{211}At -labeled chimeric 81C6 was found to be 1.24 $\mu\text{Ci/g}$ body weight in females and 2.74 $\mu\text{Ci/g}$ in males, equivalent to intravenous patient doses of 71.89 mCi in females and 191.89 mCi in males.^[45]

Eighteen patients received single doses of 10 mg of ^{211}At -labeled chimeric 81C6 mAb labeled with escalating doses of ^{211}At (2–10 mCi) via the tumor resection cavity. Serial gamma camera imaging and blood sampling performed over the first 24 h after injection showed slow leakage of ^{211}At from the cavity. $96.7\% \pm 3.6\%$ of ^{211}At decays within the cavity, and the maximum activity found in the blood pool was $0.26\% \pm 0.43\%$ of the injected dose.

The average radiation absorbed dose delivered to the tumor cavity margin was 2764 Gy (range 155–35,000) due to varying cavity volumes for these patients (0.2–37.2 cm^3). Results were encouraging with 3 patients surviving better than that achievable with conventional treatments.

Ovarian cancer

Several monoclonal antibodies are noted to be effective in the treatment of tumors from ovarian origin. These include HMFG1, HMFG2 (mouse IgG1 antibodies directed against a large mucin-like molecule expressed by the majority (>90%) of ovarian, breast, and other carcinomas; AUA1 (mouse IgG1 detects an antigen expressed by a wide range of adenocarcinomas, including the majority (>90%) of carcinomas of the ovary and H17E2 (mouse IgG1 directed against placental and placental-like alkaline phosphatase, which is expressed as a surface membrane antigen in 60%–85% of ovarian carcinomas.

In a study by Epenetos *et al*,^[46] 24 patients with advanced ovarian cancer were treated with ^{131}I -labeled monoclonal antibodies either singly or in combination. In part 1 of the study, 1.0 mCi of ^{131}I -labeled antibody was injected intraperitoneally and was washed with 1–2 L of normal saline. Gamma camera scans and blood samples were taken immediately and daily for 5 days after injection for pharmacokinetic and biodistribution analyses. Part 2 of the study involved the intraperitoneal injection of higher amounts of radiolabeled antibodies (20–205 mCi) washed with 1–2 L normal saline. This was performed 5 days after part 1 to avoid the onset of immune response against mouse immunoglobulin. Monoclonal antibodies were labeled to specific activity ranging between 4 and 8 mCi/mg. Results showed that patients treated with higher doses of radioactivity (>140 mCi) were less likely to develop progressive disease.

Pharmacokinetic data showed a whole body clearance half-life of 38–60 h in nonimmunized patients and a half-life of 20–30 h in patients who had prior exposure to monoclonal antibodies and has developed a HAMA response. The effective half-life of radiolabel on tumor cells was approximately 50 h. Most of the radioactivity was cleared by renal excretion. Dosimetry in patients with small-volume disease <2 cm in diameter indicated

that 150 mCi of radiolabeled antibody could deliver more than 8000 cGy to tumor cells. Radiation doses would be correspondingly less in patients with large-volume disease, or in patients receiving <150 mCi. Doses to bladder from 150mCi ¹³¹I-labeled antibody were calculated as being 600 cGy. No mortality from administered radiolabelled monoclonal antibody and no hematological toxicity were noted. Comparatively, the maximal tolerated whole abdomen dose by external beam is 30 Gy in 20 fractions, with a 5% incidence of complications.

Prostate cancer

Prostate cancer is a radioresponsive tumor and is a potential candidate for RIT. It typically develops small-volume micrometastases in the bone marrow and lymph nodes that will receive high levels of radiolabelled antibody. The most well established, prostate restricted, cell surface antigen is prostate-specific membrane antigen (PMSA).^[47] PMSA is an ideal antigenic target being expressed by all prostate cancers (up to 10⁶ sites per cell) and its expression levels increase in more poorly differentiated, metastatic, and hormone-refractory prostate cancers.

J591 is the deimmunized (by specific deletion of human B- and T-cell recognized epitopes) monoclonal antibody, which specifically binds with high affinity to the extracellular domain of PSMA.^[48] The PSMA-J591 antibody complex (DOTA-J591) is internalized, thereby delivering any radiolabeled antibody to the interior of the targeted cancer cells. Radiolabeled J591 with ⁹⁰Y or ¹⁷⁷Lu has been shown to have significant objective antitumor responses, including reduction or stabilization of serum PSA and decrease in tumor volume with a well-tolerated safety profile. Serious toxicity was confined to reversible myelosuppression. Optimal tumor size for treatment using the higher energy beta of ⁹⁰Y is 28-42 mm, while that for the lower energy beta of ¹⁷⁷Lu is 1.2-3.0 mm based on RIT modeling.

A prior dose escalation study using the radionuclides ⁹⁰Y- and ¹⁷⁷Lu-labeled J591 monoclonal antibodies was performed by Vallabhajosula *et al.*^[49] ¹⁷⁷Lu activity ranging from 10 to 75 mCi/m² and with ⁹⁰Y-J591, the ⁹⁰Y dose ranged from 5 to 20 mCi/m². Cold J591 (unconjugated) antibody was added to give a constant protein dose of 10 mg/m² with the ¹⁷⁷Lu dose and a total of 20 mg with ⁹⁰Y-J591 dose.

With ¹⁷⁷Lu-labeled DOTA-J591, the MTD was 70 mCi/m² as a single administration due to hematologic toxicity. Pharmacokinetic and biochemical studies were performed via venous blood sampling and total body images using a gamma camera, respectively.

The percent injected dose in major organs (heart, liver, spleen, kidneys, bone marrow, GI tract, and bladder) was estimated by drawing relevant regions of interests and calculating the relative counts in each organ compared with a standard. Using values obtained from sequential biodistribution studies and plasma pharmacokinetics, radiation dosimetry of ¹⁷⁷Lu-J591 was estimated by substituting the physical characteristics of ¹⁷⁷Lu. The critical organ with highest radiation dose is liver (7.8 ± 2.2 cGy/mCi), followed by spleen and kidneys. This is below the acceptable radiation limits of the liver. Few patients developed transient elevations of liver enzymes and were otherwise asymptomatic. The radiation dose to bone marrow based on blood radioactivity is 1.2 ± 0.4 cGy/mCi of ¹⁷⁷Lu administered. Interestingly, fractionating the administered dose with multiple doses of 30 mCi/m² was relatively better tolerated with 4 patients receiving cumulative doses up to 90 mCi/m².

In the case of ⁹⁰Y-labeled antibody, the MTD in a phase I dose escalation study^[50] was 17.5 mCi/m² with half of the enrolled patients going on to receive multiple (2-3) doses of the radiolabeled antibodies with no dose limiting toxicity. No patient developed a human anti-J591 antibody response to deimmunized J591 regardless of number of doses.

Colon carcinoma

Monoclonal antibody (mAb) A33, a murine immunoglobulin G2a (IgG2a), specifically targets the A33 antigen. A33 antigen expression is restricted to normal colon and distal small-bowel epithelium in immunohistochemical analysis of normal and malignant tissues and is homogeneously expressed in more than 95% of cases of carcinomas that originate from colonic mucosa. As with the PMSA antigen, nonsecretion of the A33 antigen; rapid internalization of the cell-bound radiolabeled mAb A33 and the expression of large amounts of A33 antigen (up to 800,000 mAb A33 molecules per cell) in colon cancer cell lines make this antigen an attractive target for selective RIT.^[51]

In a phase I/II study of ¹²⁵I-labeled A33 by Welt *et al.*^[52] patients were treated with dose escalations, starting at 50 mCi/m² with 50 mCi/m² increments for each dose level. Each dose also contained 10 mCi ¹³¹I-mAb A33. ¹³¹I WB and SPECT scans were performed together with ¹²⁵I spot views. Pharmacokinetic studies with serial blood samples were performed to monitor radiolabeled antibody levels. Despite doses greater than 700 mCi being administered, no dose-limiting toxicity was observed in any patient up to a maximum dose of 350 mCi/m² of ¹²⁵I-labeled A33. A single cell level dosimetry model that showed that the marrow dose from ¹²⁵I coupled with mAb circulating in the blood was considerably lower than previously

estimated and postulated to be due to the shielding effects of the cytoplasm of hematopoietic precursor cells from weak electron emissions that originate from circulating ^{125}I .

Binding of mAb A33 leads to internalization of the radionuclide into vesicles within the tumor cell cytoplasm *in vivo* and thereby delivering the short-range electron emissions of ^{125}I to the nucleus. In addition, higher therapeutic ratio with ^{125}I is contributed by increased circulation time, increased mAb fraction localized to tumor, and the relative marrow-sparing dose effect of ^{125}I .

Pharmacokinetic studies of radioiodinated mAb A33 from these patients achieved peak serum levels of greater than 200 pCi/mL of ^{125}I -mAb A33 and maintained levels of greater than 10 pCi/mL of ^{125}I -mAb A33 for up to 1 week. Human colon cancer cells cultured in the presence of as little as 10pCi/mL of ^{125}I -mAb A33 are killed *in vitro*.^[53] For ^{131}I -labeled mAbs, including ^{131}I -mAb A33, the MTD has been approximately 75 mCi/m² in heavily pretreated patients.

Renal cell carcinoma

cG250 is a high-affinity chimeric, IgG1 mAb, reactive with the G250 antigen. This antigen has been identified as carbonic anhydrase isoenzyme 9, a transmembranous glycoprotein, which is expressed on the cell surface of the majority (>95%) of clear cell-type renal cell carcinomas.

Oosterwijk *et al*^[54] showed the ability of radioiodinated murine antibody G250 to guide potentially high doses of radioactivity to renal cell carcinoma lesions. Earlier studies established the MTD in patients with progressive metastatic renal cell carcinoma at 2220 MBq (60 mCi)/m² ^{131}I cG250.

In a study by Brouwers *et al*,^[55] to define therapeutic efficacy, safety, and toxicity of 2 sequential high-dose treatments of RIT with ^{131}I cG250 in patients with metastasized renal cell carcinoma, 2 sequential administrations of therapeutic ^{131}I cG250 was given to patients. For individual dosing, each RIT treatment is preceded by a tracer (low-activity dose) infusion of the radiolabeled mAb, followed by γ -radiation measurements and dosimetric calculations.

Dosimetric analysis of scintigraphic images following diagnostic doses was done using conjugated views counting technique with partial background subtraction and correction for attenuation and physical decay with ROIs over the whole body, critical organs, and metastases. Organs of interest, showing retention of the radiolabeled antibody on the anterior and posterior scintigraphic images, were lungs, heart, liver, spleen,

remaining kidney, and thyroid. Only metastatic lesions that were identified and measurable on CT and visualized on the scintigraphic images were analyzed. The activity in all ROIs was expressed as percentage of the total injected dose. Residence times of activity in WB and organs of interest were calculated using monoexponential curve fitting. Radiation absorbed doses to organs and metastases were calculated with the MIRDOSE3 program while residence time of and the radiation-absorbed dose to the bone marrow were calculated by a blood-derived method.

Estimated mean radiation-absorbed dose of ^{131}I cG250 in total body, organs, and metastases based on the images acquired after the first diagnostic ^{131}I cG250 infusion were as follows: 0.28 ± 0.03 Gy in males and 0.36 ± 0.04 Gy in female whole bodies, $0.22\text{--}2.21 \pm 0.76$ Gy in males and $0.34\text{--}2.36 \pm 0.67$ Gy in females (the dose ranges received by the thyroid, spleen, and kidneys with descending order for both sexes); 2.09 ± 2.67 Gy for males and 13.1 ± 23.1 Gy for metastases in females.

In normal tissues, the calculated absorbed dose based on the first diagnostic infusion of ^{131}I cG250 was highly similar to the calculated absorbed dose based on the second diagnostic infusion administered 3 months later.

Visually, the highest uptake was observed in thyroid and metastatic lesions which corroborated with the quantitatively determined highest radiation-absorbed doses. Absorbed dose in metastases varied widely but did not exceed 10 Gy for most lesions, well below the minimum of 50 Gy considered to be required for a therapeutic response in most malignancies. A significant inverse relation was noted between absorbed doses and weight of the metastatic lesions with the highest radiation-absorbed doses localizing to smaller metastases. This, however, was not commensurate with a better response percentage of these lesions as no difference in response or tumor stabilization was seen between small and larger metastases

WB radiation-absorbed dose measured with the γ -probe (as described by Divgi *et al*,^[56]) after administration of ^{131}I cG250 was in good agreement with the radiation absorbed dose to the WB estimated by MIRDOSE3-based estimates using the ROI of the WB. There was a good correlation between the clearance rates of the radiolabel derived from blood sampling and $t_{1/2}$ eff derived from the probe measurements after both RITs.

No correlation was observed between the hematopoietic toxicity noted and the radiation-absorbed dose to the bone marrow, the absorbed dose to WB, or the administered activity.^[55] Thus the authors concluded that activity dosing based on conventional dosimetric analysis of a

tracer injection that adequately predicts susceptibility for significant hematologic toxicity is not feasible.^[57] Dosing of the administered radioactivity based on body surface area at MTD resulted in hematologic toxicities. The MTD was determined to be 75–90 mCi/m² of ¹³¹I. It was also not possible to predict hematologic toxicity for individual patients treated with 2 RITs of ¹³¹IcG250.

Selective Internal Radiation Therapy with Y-90 Microspheres

Therapy with ⁹⁰Y-microspheres is emerging as a mainstream treatment modality in the management of patients with primary and metastatic liver cancer. This “internal radiotherapy” for hepatocellular carcinoma (HCC) or metastatic hepatic lesions is based on the observation that hypervascular tumors have a differential arteriolar density of tumor relative to adjacent noncancerous tissue. Commercially available ⁹⁰Y-microsphere products include resin microspheres with a specific activity of 1081–1891.9pCi (40–70 Bq) per sphere (SIR-Spheres) and glass microspheres with a specific activity of 0.064–0.073 μCi (2400–2700 Bq) per sphere (TheraSphere). Radiation delivery from ⁹⁰Y-microspheres is essentially confined to the liver because of the 3.8 mm mean range and approximately 10 mm maximum range of β-particles in soft tissue.⁹⁰Y has a long β range that hampers irradiation of small tumors, but irradiates more uniformly larger tumors that often display heterogeneous perfusion.^[58] ⁹⁰Y-microsphere distribution is invariably patchy and heterogeneous, with a wide range of variation. MIRD dose estimations, however, are based on the assumption of a uniform distribution. Despite this limitation, the MIRD methodology provides consistent and reproducible dose estimates.^[58,59] The administered ⁹⁰Y-microsphere activity is distributed in tumor and normal liver compartments. The distribution profile is determined by the relative vascularity and volume of these 2 compartments and is expressed as the tumor-to-liver ratio (TLR). When lung shunting due to intrahepatic peritumoral arteriovenous communications occurs, a third compartment (lung) is encountered and is expressed as the lung shunt fraction (LSF). The TLR and LSF can be determined using ^{99m}Tc-macroaggregated albumin scans. Region of interest analysis of tumor and normal liver compartments on SPECT images is used to determine the TLR. The LSF can be similarly calculated on planar images again using a mathematical formula. For shunt volumes that exceed 10%, dose reduction is performed because of the higher risk of radiation pneumonitis (10%–15% shunt volume: calculated dose minus 20%; 15%–20% shunt volume: calculated dose minus 40%). Shunt fractions greater than 20% is an exclusion criterion.^[58] Animal studies employed a dose-escalation design with injections of

up to 12 times (on a liver weight basis) the anticipated human dose. These results yielded a proposed human radiation exposure range of 50–100 Gy. The tolerance limit of the normal human liver for SIRT proposed by Fox *et al.* was 80 Gy.^[60] Administered activity of ⁹⁰Y-labeled microspheres can be based on an empiric dose or calculated by the partition method. Assuming the relative distribution of ^{99m}Tc-MAA is similar to that of ⁹⁰Y-labeled microspheres, tumor and nontumor radiation doses can be calculated using the percentage of lung shunting and tumor to nontumor ratio determined from the pre-therapeutic ^{99m}TcMAA scan. Using this partition model, Ho *et al* was able to estimate radiation doses for normal liver parenchyma and hepatic tumors.^[61,62] Empiric administered activity of SIR-Spheres can also be adapted to the estimated tumor load of the liver based on empiric calculation: <25% liver replacement: 54.05 mCi; 25%–50% liver replacement: 67.56 mCi; >50% liver replacement: 81.08 mCi. Radiation pneumonitis is a concern with hepatic-directed radiation treatment.^[63] Previous preclinical and clinical studies with ⁹⁰Y-labeled microspheres demonstrated that up to 30 Gy to the lungs could be tolerated with a single injection, and up to 50 Gy for multiple injections.

Lipiodol Therapy for Hepatocellular Carcinoma

Lipiodol consists of mono-, di-, and tri-iodinated ethyl esters of linoleic, oleic, and stearic acids, 38% of which contains natural iodine. Selective retention of iodized oil in hepatocellular carcinoma following its injection into the hepatic artery was first established by Nakakuma *et al.*^[64] Lipiodol is retained by HCC for longer periods ranging from several weeks to over a year, while it is rapidly cleared from the normal liver parenchyma within 7 days. Internal radiation therapy is possible when some of the iodide present in the lipiodol is substituted by ¹³¹I using a nuclidic exchange reaction. This treatment is not only used for palliation but can be curative when the ¹³¹I-lipiodol is given as neoadjuvant therapy before liver transplantation and/or after resection of HCC. Aside from the hepatic tumor, ¹³¹I-lipiodol is mainly taken up by the lungs and the normal liver.

A dosimetric study performed by Monsieurs *et al*^[65] revealed calculated absorbed dose (according to the MIRDose program) for the total body was 0.97 Gy (SD 0.23, range, 0.65–1.27). Mean absorbed doses were 6.70 Gy (SD 1.88, range 3.05–11.08) for the normal liver, 144.4 Gy (SD 68.5, range 69–288) for the tumor and 6.5 Gy (SD 3.4, range, 0.8–11.6) for the lungs. The mean effective dose for the patient calculated from the weighted contributions of the organs was 2.05 Sv (SD,

0.59; range, 0.93–2.94). The mean absorbed dose for the most relevant organs was comparable using the Monte Carlo simulation program MCNP-4B (mean absorbed dose to the tumor calculated with the MCNP software was 129.5).

A study of transarterial rhenium-188 HDD lipiodol treatment of inoperable primary hepatocellular carcinoma was reported by Sundram *et al.*^[66-68] The initial infusion of 5.4 mCi was performed as a scout dose for dosimetric calculation. Both anterior and posterior images were obtained to calculate geometric mean counts with ROIs placed over lung, liver, and tumor. Counts per pixel were obtained to calculate maximum tolerated activity to liver and lung. The mean treatment dose activity was 124 mCi of ¹⁸⁸Re-lipiodol with a range of 50–265 mCi. For dosimetric purposes, cumulated radioconjugate activities were calculated assuming elimination of activity only by physical decay in situ. The radiation absorbed doses to the therapy-limiting normal tissues, liver, lung, and red marrow were calculated using the MIRD schema and adjusting the pertinent S factors.

Based on maximum tolerated absorbed doses of 30, 12, and 1.5 Gy to liver, lung, and red marrow, respectively, the respective absorbed doses per unit administered activity were used to calculate the MTD. These doses had been found to be safe in multiple trials using external beam therapy but not confirmed for systemically administered radiopharmaceuticals. Results showed that the bone marrow radiation doses are negligible and the radiation doses to the lung are also small. The main limiting factor to higher dose ¹⁸⁸Re-lipiodol treatment appears to be the MTD to normal liver.

Peptide Receptor Radionuclide Therapy

⁹⁰Y-DOTATOC, ⁹⁰Y-DOTATATE, and ⁹⁰Y-lanreotide are the principal ⁹⁰Y-labeled radiopharmaceuticals used for PRRT. A major disadvantage of ⁹⁰Y-labeled peptides is the lack of γ -emission, which makes it difficult to get specific dosimetry in each patient. To estimate a specific dose, alternative methods such as imaging with analogs labeled with ¹¹¹In or substituting the positron emitter ⁹⁰Y with ⁸⁶Y may be used. With ⁹⁰Y, reported toxicity was mainly renal, with a significant impairment of renal function and some patients evolving to end-stage renal failure and hemodialysis. With dose escalation, however, bone marrow irradiation levels may become critical and also may lead to delayed myelotoxicity. The major drawback of ⁹⁰Y-peptides is that the activity administered is limited by the high renal dose, which can preclude the achievement of a prescribed tumor dose. The high affinity

of the peptide for its receptor and the internalization of the receptor-peptide complex facilitate retention of the radionuclide in receptor expressing tumors, whereas its relatively small size facilitates rapid clearance from the blood. Pauwels *et al* treated a series of 60 patients after individual kidney dose estimation using ⁸⁶Y-DOTATOC imaging and the MIRDOSE3.1 model. Despite activities administered to each patient being calculated so that the expected doses delivered to the kidneys would not exceed a fixed limit of 27 Gy, various degrees of nephropathy were experienced by 5 patients, with 1 patient on hemodialysis at a 5-year follow-up.^[69] The MIRDOSE model referred to standard kidney volumes for males and females (288 and 264 mL, respectively). Instead, taking the actual renal volume measured by CT into account resulted in a median undercorrection of the absorbed dose by 11%. The actual dose to the glomeruli may be twice that estimated with the classic MIRD model based on fixed kidney size and homogeneous activity distribution within the whole organ. In a recent improvement of the MIRD model, Bouchet *et al*^[70] proposed a multiregion model for the kidney, including 4 main homogeneous regions as source/target: cortex, medulla, pelvis, and papillae. The kidney dose estimates could be made more patient specific by rescaling the 4 kidney regions on the basis of the actual kidney volume measured by CT or MRI. To make use of this model, it is essential to know the activity distribution inside the kidney evaluated by PET and SPECT cameras or more accurately, by voxel-based methods.^[71] ¹⁷⁷Lu-labeled peptides demonstrate characteristics that enable imaging and therapy with the same complex and allow dosimetry to be performed before and during treatment as well. Its penetration range in tissue (maximum range, 2 mm) indicates a lower cross-fire effect compensated by a higher percentage of the radiation energy absorbed in very small volumes and making ¹⁷⁷Lu a good candidate nuclide for the treatment of small tumors (<2 cm) and micrometastases with ¹⁷⁷Lu-DOTATATE. Dosimetric data on ¹⁷⁷Lu-DOTATATE are limited.^[72] The blood clearance and urinary excretion are fast, similar to the other somatostatin analogs and the dosimetry of normal organs is lower for ¹⁷⁷Lu-DOTATATE compared with ⁹⁰Y-DOTATOC.

Issues and Recent Advances

The determination of source organ activities over time is usually achieved by interpolation between the data collected at specific time points and further extrapolation to infinity beyond the last measurement. For generation of such time-activity curves, a set of linear and exponential segments or a smooth curve derived from a compartment model can be used. To minimize the risk of an inaccurate extrapolation that could lead to significant under- or overestimation of the dose to

target organs, it is recommended that data points be collected to cover 3 effective half-lives of the therapeutic compound. Alternatively, a conservative approach may be chosen by assuming that, beyond the last measurable time point, the compound is retained in the organ and that the activity is declining only by radioactive decay. In radionuclide therapies of follicular lymphoma and in PRRT, pretherapy dosimetry has been performed with tositumomab and somatostatin receptor peptides/DOTA-compounds labeled with indium-111. Its longer half-life allows dosimetric data to be obtained by assessing its pharmacokinetics over at least 3 half-lives and gamma emissions from ^{111}In have the advantage of allowing scintigraphic images to be acquired. However, this has its disadvantages. Substituting ^{111}In for ^{90}Y was shown to induce structural changes in somatostatin analogs that may affect the receptor binding affinity and end up in significantly different biodistributions.^[73] For antibodies, it is commonly admitted that the labeling with ^{111}In does only slightly affect the biodistribution, although, depending on the antibody used, some authors reported a considerable increase^[74] or decrease^[75] of the marrow uptake measurement.

The traditional use of the MIRD schema was in its application to diagnostic radiopharmaceuticals. Its implicit assumptions that radioactivity and accumulated activity were uniformly distributed within organ size source regions and that radiation energy is uniformly distributed within organ size target regions. Another flaw of the traditional MIRD model was the basis of average time-activity data in animal models or small cohorts of human subjects and use of age- and sex-specific "average/standardized" models of human anatomy. Tumors were not incorporated into the MIRD schema as either source or target regions. Patients deviate kinetically and anatomically from the respective kinetic and anatomic averages, thus making tissue dose estimates inaccurate. With therapeutic radiopharmaceuticals, the risk to benefit ratio for receiving radiation are dramatically small and tolerances for inaccuracies in dose estimation are greatly reduced. Once the time integrals of activities in organs of interest are measured, absorbed dose calculations in target organs can be performed using dedicated software, such as the MIRDOSE program, in which S values from any source to any target are integrated. Although age- and sex-specific reference data for human anatomy are included in the program, the estimated doses derived are far from patient-specific or even accurate, because they take into account neither patient-specific differences in organ shape or size nor nonuniform distribution of activity within the source organs. To improve the accuracy of activity to dose conversion, more sophisticated methods may include actual organ shape and size, nonhomogeneous activity distributions, fused SPECT/CT and PET/CT images,

and Monte Carlo algorithm codes.

Positron emitters allow the use of PET imaging that provides increased quantitative accuracy and spatial resolution. ^{86}Y PET was developed and provided probative results in dosimetry assessment. Unfortunately, the decay characteristics of ^{86}Y inherently have a drawback that requires careful attention. ^{86}Y emits a high number of prompt γ -rays responsible for overestimations of activity that may reach 100% and 80% in the background and kidneys, respectively, when not properly accounted for. This is particularly true in 3-dimensional mode acquisition. Sophisticated correction methods are required to obtain accurate dosimetric quantification. However, radiopharmaceutical grade ^{86}Y is not commercially available and requires a 16-MeV cyclotron for its production.

Planar image acquisitions in dosimetric calculations should be avoided, because they do not allow the actual delineation of organs of interest. Significant improvement in accuracy of measured doses may be achieved by precise organ volume measurement with the use of high-spatial-resolution techniques, such as CT or MRI and newer functional imaging techniques with PET/CT and SPECT/CT.

New therapy perspectives pursue the use of combination radionuclide therapy, such as the use of ^{177}Lu - and ^{90}Y -radiopeptides, as a promising treatment for somatostatin receptor expressing tumors of different-sized lesions. This was confirmed in an animal model, where a cocktail of ^{90}Y - and ^{177}Lu -labelled somatostatin analogs showed better tumor response than the use of each radioisotope alone.^[76] Accurate dosimetry in this context is even more of an importance to avoid normal organ toxicity. This can be extrapolated to other tumor types where combinational therapies using different radiopharmaceuticals (utilizing their unique characteristics) to treat tumors of varying sizes.

Radiation-induced organ toxicity is a significant problem in any radionuclide therapy. In a recent review article, Vegt *et al*^[77] described several mechanisms of renal toxicity and methods to reduce this radiation burden to the kidneys. Coinfusion of basic amino acids is currently the standard renoprotective regimen in clinical PRRT. The combination of 25 g of lysine and 25 g of arginine was more effective than 50 g of lysine and caused relatively few side effects. The highest dose of 75 g of lysine was most effective in reducing renal uptake but frequently caused side effects, such as vomiting.^[78] Most strategies for the reduction of kidney damage in PRRT and RIT have not been widely tested on patients. Further indepth research, especially on the combination strategies to reduce renal toxicity is needed.

Dose fractionation or multiple dosing maybe a practical strategy to decrease bone marrow radiation dose while increasing cumulative dose to the tumor at an optimal dose rate. Preclinical data have shown that dose fractionation or multiple low-dose treatments can decrease toxicity while increasing the efficacy. However, waiting for hematologic recovery from prior treatment doses before delivering the next dose may allow tumor progression. Further clinical studies to verify this are needed.

Although much effort and advancements have been made in the field of dosimetry for targeted radionuclide therapies, the above-mentioned factors should be considered in any radionuclide therapy program for successful treatment of patients. Patient-specific dosimetry should be performed in all patients with the aim of maximizing radiation dose to tumor and minimizing absorbed dose to normal tissues and organs. Subsequent studies on dosimetry for targeted radionuclide therapies should make use of the 3D advantages of SPECT/CT and PET/CT in estimating tumor absorbed doses as well as using the CT component for accurate tumor or organ volume calculation.

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