Radiation Dosimetry for Radionuclide Therapy in a Nonmyeloablative Strategy

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“Targeted, continuous low dose rate radiotherapy is neither conventional radiotherapy nor chemotherapy.”

Radionuclide therapy extends the usefulness of radiation from localized disease to multifocal disease by combining radionuclides with disease-seeking drugs, such as antibodies or custom-designed synthetic agents. Like conventional radiotherapy, the effectiveness of targeted radionuclides is ultimately limited by the amount of undesired radiation given to a critical, dose-limiting normal tissue, most often the bone marrow. Because radionuclide therapy relies on biological delivery of radiation, its optimization and characterization are necessarily different than for conventional radiation therapy. However, the principals of radiobiology and of absorbed radiation dose remain important for predicting radiation effects. Fortunately, most radionuclides emit gamma rays that allow the measurement of isotope concentrations in both tumor and normal tissues in the body. By administering a small “test dose” of the intended therapeutic drug, the clinician can predict the radiation dose distribution in the patient. This can serve as a basis to predict therapy effectiveness, optimize drug selection, and select the appropriate drug dose, in order to provide the safest, most effective treatment for each patient. Although treatment planning for individual patients based upon tracer radiation dosimetry is an attractive concept and opportunity, practical considerations may dictate simpler solutions under some circumstances. There is agreement that radiation dosimetry (radiation absorbed dose distribution, cGy) should be utilized to establish the safety of a specific radionuclide drug during drug development, but it is less generally accepted that absorbed radiation dose should be used to determine the dose of radionuclide (radioactivity, GBq) to be administered to a specific patient (i.e., radiation dose-based therapy). However, radiation dosimetry can always be utilized as a tool for developing drugs, assessing clinical results, and establishing the safety of a specific radionuclide drug. Bone marrow dosimetry continues to be a “work in progress.” Blood-derived and/or body-derived marrow dosimetry may be acceptable under specific conditions but clearly do not account for marrow and skeletal targeting of radionuclide. Marrow dosimetry can be expected to improve significantly but no method for marrow dosimetry seems likely to account for decreased bone marrow reserve.

Key Words: Radionuclide, dosimetry, therapy, radiotherapy, cancer

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INTRODUCTION

Radionuclides provide powerful vehicles for delivering radiotherapy to treat metastatic cancer. Dependent on the delivery vehicle (drug), radionuclides can preferentially deliver a radiation dose that is orders of magnitude (10–10,000 times) greater to all disease sites than that delivered to normal tissues, after a single intravenous administration. Indeed, the microscopic cellular and subcellular radiation doses delivered to the diseased tissue can be even greater than reflected by the macroscopic radiation dose, using selective targeting vehicles. Nevertheless, radionuclide therapy, like other radiotherapies, is ultimately limited by undesired radiation to a critical, dose-limiting, normal tissue, usually the bone marrow.

Another unique aspect of radionuclide therapy is its continuous nature, similar to sealed radionuclide source radiotherapy, excepting for its lower dose rate. The continuous nature of the radiation leads to cells being more likely to be caught in the highly radiosensitive G2/M phase of the cell cycle. Additionally, the effectiveness of low dose rate radiation is not affected as much by hypoxia as is high dose rate radiation. Low dose rate radiation leads to cell death through apoptotic mechanisms rather than through interruption of cell proliferation.  

Finally, radionuclide therapy is unique compared to other drug-based treatments because it provides the opportunity to generate a fore-knowledge of the radionuclide drug pharmacokinetics and radiation dose distribution. Thus, the likely toxicity (adverse events) and efficacy to be expected can be estimated using a tracer amount of the intended therapeutic drug. This approach can be used to establish the safety and efficacy of the therapeutic drug during the developmental phase, and can also be used for predictions of toxicity and efficacy, or for development of a treatment plan, for an individual patient.

Ideally, radiation dosimetry for radionuclide therapy would allow the physician to estimate absorbed radiation dose to the patient in a way that is meaningful for predicting radiation effects in both tumor and normal tissue. Accomplishing this involves quantitative estimation of radionuclide distributions in the patient, characterization of the patient’s anatomy, and estimation of the biological characteristics that influence the translation of absorbed radiation dose into tumor response and tissue injury. These components are shown schematically in Figure 1. The usefulness of radiation dosimetry for radionuclide therapy depends on the combined accuracy of all of these components, and is ultimately judged by the reliability with which it allows the clinician to optimize individual patient treatments and clinical trials.

So far, internal radiation dosimetry has been highly successful for ensuring safety for the relatively low levels of activity associated with diagnostic radiotracers. However, radiation dosimetry for the much-higher therapeutic doses remains a challenge, especially in the context of dose-limiting tissues such as bone marrow, whose volume, structure, and functional reserve are important and hard-to-measure factors for estimating and reliably translating absorbed radiation dose into biological effects.

In summary, radionuclide pharmacokinetics and radiation dosimetry can be useful for: 1) drug
development; 2) predictions of toxicity and efficacy; and, 3) patient-specific dosing and treatment planning. Other uses for radiation dosimetry include application to future radiotherapy decisions for the patient and interpretation of late adverse and epidemiologic events.

RADIONUCLIDE IMAGING AND RADIATION DOSIMETRY FOR TREATMENT PLANNING

Radionuclide therapy is inextricably linked to radionuclide imaging. In contrast to other therapies, the safety of a radionuclide drug can be readily established during the developmental phase, using a tracer amount of the drug. Absence, or quantitation of the amount, of drug localization in normal tissues can readily be established. Similarly, specific (selective targeting) or preferential localization in the diseased (cancerous) tissue can also be documented. A greater challenge for radionuclide therapy is to accurately estimate the absorbed radiation dose distribution for an individual patient. This process involves two levels of sophistication: quantifying the amount of radionuclide administered/decayed/excreted and imaging its 2- or 3-dimensional distribution in the body as a function of time. Obtaining sufficiently accurate quantitative images of activity in the body remains a demanding requirement due to the need for correction methods for the effects of radiation attenuation and scatter in both the patient and detector system, as well as limitations imposed by detector efficiency and image resolution. Another continuing challenge is to accurately model radioactive source kinetics in the body. This has been done using direct integration, least squares analysis, and compartmental modeling.

In order to obtain meaningful estimates of radiation dose, information about the time-dependent characteristics of the radionuclide distribution must be combined with a model of the patient’s anatomy. Descriptions of patient anatomy range from mass/surface area to cylinder/ellipsoid “standard man” approximation to individualized patient anatomy based on computed tomography or magnetic resonance imaging. For patient-scale localization, underlying anatomical imaging technology has been well developed for other diagnostic purposes, and the primary challenge for radionuclide therapy is to fully utilize the information available. Bone marrow dosimetry for radionuclide drugs that bind to cellular components of bone, marrow, or blood introduce the importance of cell-level dosimetry in order to accurately predict toxicity, as described by Sgouros et al. Specific dosimetry methods and challenges for bone marrow are described in detail later in this paper.

With radionuclide distribution and patient anatomy established, several methods and computerized software systems have been developed for estimating radiation dose in the patient. These range from reference tables derived from cylinder/ellipsoid “standard man” model calculations to point-kernel approaches to stochastic (Monte Carlo) simulation of radiation dose deposition in the patient. Questions about the patient-specific accuracy of currently-used dose calculation methods remain. Also, the potential of Monte Carlo radiation transport in terms of simultaneously calculating dose and improving the accuracy of activity distribution estimates has remained untapped in the context of practical patient trials.

Put together, these pieces form the basis of a treatment planning system for radionuclide therapy. The goal of a treatment planning system is to provide the physician with pretreatment information that will allow the physician to plan (and optimize) the patient’s treatment. This means determining in advance the amount of dose to dose-limiting organs per MBq of drug administered, so that the physician administers the appropriate amount of drug for each patient. In addition to allowing the physician to plan treatments, the treatment planning system, when combined with relevant input data collected during the treatment, allows retrospective analysis of doses (and dose rates) delivered during treatment, and their relationships to outcomes.

DOSIMETRY IN DRUG DEVELOPMENT

Radionuclide therapy is unique because the drug pharmacokinetics and radiation dose distribution can be estimated for an individual patient using a tracer amount of the drug intended for subsequent therapy. Radiation dosimetry for radionuclide therapies has not yet reached the sophistication of radiation dosimetry for external beam and sealed source radiotherapy. Until recently, radionuclide dosimetry for radionuclide therapies was determined using the concept of a reference man (woman or child). For applications to
drug development, this approach may be adequate. More recently, the spatial characteristics of the specific patient and the energy distribution of the specific radionuclide have been used to generate patient-specific radiation dosimetry. These approaches are required for applications that address individual patients rather than patient cohorts.

Using tracer amounts of radionuclide, the pharmacokinetics and radiation dosimetry of differing radionuclide drugs may be compared in order to evaluate their relative advantages (Figures 2–4). Comparisons of pharmacokinetics and radiation dosimetry based on safe tracer studies in small numbers of patients are of great importance when assessing differing drugs, radionuclides, or conjugation methods intended for the same purpose. Radiation dosimetry can also be estimated “after the fact” for the treatment dose in order to retrospectively assess the relationships between predicted, and realized, absorbed radiation dose distributions and efficacy or toxicity.

There is little doubt that radiation dosimetry is required in phase I dose-finding studies, and probably also in phase II studies (at some of the multiple participating institutions) to reinforce the validity of the phase I dosimetry data and to provide toxicity/efficacy comparisons, even if radionuclide dosing is based on methods other than a tracer study for treatment planning. Radiation dosimetry in phase I, II studies permits acute and late toxicities to be related to the radiation dose delivered to the normal tissues and predictive risks to be determined for various treatment plans. In the same manner, tumor response can be predicted on the basis of the estimated tumor radiation dose. Importantly, these studies provide quantitative information on the interpatient variability of drug pharmacokinetics, a critical factor for subsequent choice of dosing method for routine use. Treatment planning strategies that provide recommendations for treatment of individual patients based upon accurate estimates of radiation dose distribution for each combination of radionuclide and targeting drug have been developed.

The following are illustrative of the use of this powerful tool. A total of 70 patients with non-Hodgkin’s lymphoma (NHL) were enrolled in trials to assess the relative merits of $^{67}$Cu-2IT-BAT-Lym-1, $^{131}$I-Lym-1 and $^{90}$Y-2IT-BAD-Lym-1 monoclonal antibody (MAb); $^{111}$In was used as an imaging surrogate for $^{90}$Y dosimetry. Cumulated activity, analogous to the “Area Under Curve” (AUC), for a drug that does not undergo physical decay of the radionuclide, was higher for tumors and normal tissues of the patients receiving $^{67}$Cu-2IT-BAT-Lym-1 or $^{111}$In-2IT-BAD-Lym-1 than for patients given $^{131}$I-Lym-1 (Figure 2). Tumor cumulated activity was greatest for $^{67}$Cu-2IT-BAT-Lym-1 because of greater retention and uptake. Liver cumulated activity was less for $^{131}$I-Lym-1 than for $^{67}$Cu-2IT-BAT-Lym-1 or $^{111}$In-2IT-BAD-Lym-1 due to shorter retention. Despite greater tumor cumulated activity of $^{67}$Cu-2IT-BAT-Lym-1, tumor radiation dose from $^{90}$Y-2IT-BAD-Lym-1 was greater than that from $^{67}$Cu-2IT-BAT-Lym-1 or $^{131}$I-Lym-1 because of the high abundance and energy of the beta emissions from $^{90}$Y. However, the potential advantage of higher tumor radiation doses for the radiometals can only be fulfilled if reflected in the therapeutic indices, that is, the ratio of tumor radiation dose to normal tissue radiation doses. Unfortunately, radiometals can also be retained in normal tissues, particularly the liver, thereby limiting the radionuclide dose that can be administered. Mean tumor-to-marrow therapeutic index was three-fold better for $^{67}$Cu-2IT-BAT-Lym-1 when compared to $^{131}$I-Lym-1 (Figure 3). Retention of radiometal labeled Lym-1 by the liver lowered their therapeutic index, so that the liver was likely to be dose-limiting in myeloablative radioimmunotherapy.

One approach to reducing radiation dose to the liver is to attach the radiometal chelate to the MAb, using a peptide linker readily metabolizable in the hepatocyte. DOTA-peptide-ChL6 has a peptide linker between DOTA and ChL6 that is susceptible in vitro to endopeptidase activity, specifically cathepsin B, a major metabolic enzyme in hepatocytes. The pharmacokinetic and dosimetric properties of the radioimmunoconjugates, $^{111}$In-, and $^{90}$Y-DOTA-peptide-ChL6 and $^{111}$In-, and $^{90}$Y-2-iminothiolane-2-[(bromoacetamido)benzyl]-DOTA-ChL6, were compared in athymic mice bearing HTB3477 human breast cancer xenografts. Each drug concentrated well in the xenografts. Liver concentration, cumulated activity and radiation dose of the DOTA-peptide-ChL6 drugs were one-third to one-half those of the corresponding 2-iminothiolane-2-[(bromoacetamido)benzyl]-DOTA-ChL6. The challenge was to obtain analogous information in patients where direct comparison may not be feasible. In a study of $^{90}$Y-labeled chimeric L6 (ChL6) MAb in patients with breast cancer, the use of a metabolizable peptide linker reduced the radiation dose to the liver by about two thirds compared to that expected for $^{90}$Y-ChL6 having a non-metabolizable linker (Figure 4).
NONMYELOABLATIVE RADIONUCLIDE THERAPY

Although there have been exceptions, the critical, normal tissue for systemic radionuclide therapies, has been the bone marrow in the absence of strategies incorporating bone marrow reconstitution (marrow and/or peripheral stem cell transplantation). Thrombocytopenia and leukopenia/neutropenia have usually been the initial and most severe manifestation of this toxicity. Although myelotoxicity has generally been dose-limiting, the degree of myelotoxicity has varied among patients given similar amounts of radionuclide, and

Figure 2. Cumulated activity concentrations (mean ± 1 std. dev., GBq-s/GBq/g) for $^{67}$Cu-, $^{131}$I-, and $^{90}$Y-Lym-1 MAb per unit of radionuclide administered to NHL patients. Cumulated activity is equivalent to the area under the time-activity curve and analogous to the AUC for a drug that does not undergo physical decay of the radionuclide. AUCs for $^{67}$Cu-Lym-1 and $^{111}$In-Lym-1 would be even higher than those for $^{131}$I-Lym-1 if corrected for radionuclide physical decay because their physical half-times are shorter than that of $^{131}$I. Marrow cumulated activity was determined by imaging three lumbar vertebrae and extrapolating for entire red marrow.

Figure 3. Therapeutic indices (ratio of tumor-to-normal tissue radiation doses per unit of administered radionuclide) for $^{67}$Cu-, $^{131}$I-, and $^{90}$Y-Lym-1 in NHL patients. Therapeutic indices (mean and range) for the patients given $^{67}$Cu-Lym-1 (n = 11 patients), were more often better than those for patients given $^{90}$Y-Lym-1 (n = 13 patients) or $^{131}$I-Lym-1 (n = 46 patients).
from one therapy dose to another in the same pa-
tient. Manifestations of myelotoxicity are likely
to be more severe if the patient has pre-ex-
isting peripheral blood cell abnormalities or the
marrow has been compromised by prior ther-
ancy.24 Larger doses of radionuclide can be given
to selected patients because they have relatively
normal peripheral blood cell counts and normo-
cellular bone marrows uninvolved by the disease.

Myelotoxicity can be assessed directly using
examination of samples of bone marrow obtained
by biopsy and indirectly using peripheral blood
counts obtained on blood samples. Beyond being
an invasive procedure for the patient, bone mar-
row biopsy provides marrow aliquots from a dis-
crete location that represent about 1/3,000 of the
total bone marrow. This leads to serious aliquot
sampling problems, particularly for localized dis-
ease processes. Peripheral blood counts represent
sampling of the blood compartment in which the
cell content represents the net result of blood cell
production in the marrow, release of these cells
into the circulation, and the survival of these cells
in the circulation. Whereas, radiation impairs
marrow cell production, many diseases, includ-
ing cancer, can inhibit or increase release of blood
cells from the marrow, or accelerate their de-
struction. Furthermore, there is a wide range of
normality for peripheral blood counts, so that low
grades of radiation myelotoxicity can occur with-
out the blood counts reaching the standards used
to grade toxicity. Contrariwise, patients with de-
creased peripheral blood counts prior to treat-
ment, perhaps due to previous treatment of their
disease, may reach gradeable levels of toxicity
without much influence from the radionuclide
therapy. Although bone marrow biopsy and per-
ipheral blood counts are fundamental to the man-
agement of patients treated with radionuclides,
alternatives are required to better judge the effect
of the radionuclide therapy on the bone marrow.

MARROW RADIATION DOSIMETRY

Using the total body as a marrow surrogate, Ben-
uet al.33 have observed that 200–400 cGy to the
marrow was the dose limit for 131I-iodide
therapy in patients with thyroid cancer. These pa-
tients do not usually have compromised bone
marrows and thyroid cancer does not usually in-
volve the marrow. Lower radiation dose to the
marrow from radionuclide labeled MABs and
peptides has produced grade 3 or higher myelo-
toxicity, as judged by blood counts; these patients
usually had heavily pretreated, advanced can-
cers.21–24,28–32,34 A number of methods for esti-
mating marrow radiation doses have been de-
veloped. Nevertheless, these models do not always
provide marrow radiation doses that strongly correlate with the clinically observed
myelotoxicity. Explanations for the discrepancies
include inadequate marrow dosimetry models,
heterogeneous patient populations, and disease
that results in drug targeting of the marrow.44–46

For radiation dose to the bone marrow to be
meaningful, all sources of marrow radiation must
be considered. The marrow can receive radiation
from the nonspecific presence of radionuclide in
its extracellular fluid, often referred to as blood
compartment or contribution, and in other nor-
tal tissues of the body, referred to as body con-
tribution. Specific uptake of radionuclide in
skeletal or marrow elements because of drug, or
radionuclide, targeting to normal marrow/bone
elements represents an additional source of radia-
tion to the bone marrow. Many cancers involve
the marrow and skeleton so that specific target-
ing of the cancer involves “spillover” of radia-
tion to normal marrow cells from therapeutic ra-
dionuclide emissions having long range.

Blood and Body Methods

Factors affecting the prediction of myelotoxicity
(determined by decreases in peripheral blood cell
counts) can be simple, such as injected dose of
radionuclide (GBq), or more complex, such as
quantitated radiation dose to marrow. In patients
without bone marrow malignancy, myelotoxicity
has been reported to increase along with injected
dose of radionuclide.47 The correlation of ad-
ministered radioactivity with myelotoxicity was
improved when total radioactivity was related to
body surface area. The Dosimetry Task Group of
the American Association of Physicists in Medi-
cine has recommended a standardized method
for calculating marrow radiation dose, using
blood radionuclide as the contributing source.39
Sgouros et al.40 recommended modification of
this method to adjust for the hematocrit of each
patient. Other investigators have associated
myelotoxicity with the total body radiation dose
in patients with NHL selected to avoid those with
substantial marrow malignancy.48 DeNardo et
al.36 have described a method for marrow radia-
tion dose that accounts for both blood and body
contributions. Radiation dose to bone marrow
from radionuclidic sources in body, blood, or both have had only modest predictive accuracy. Confounding factors include prior chemotherapy, the malignancy itself, and age. The recommendations of the Dosimetry Task Group for blood-derived estimates for marrow radiation dose are valid only if specific marrow uptake due to targeting of normal or abnormal (malignant) marrow elements is absent. In patients with hematopoietic and other malignancies, marrow involvement is common. Radiation dose to the marrow from radionuclide targeted to malignant cells in the marrow and skeleton can be significant, and is evaluable by bone marrow biopsy and by radionuclide imaging. Tardivon et al. have shown that magnetic resonance imaging revealed NHL in the marrow even when marrow biopsies were negative.

**Imaging Methods**

Several groups have described imaging methods for measuring the marrow radiation from targeted radionuclide. Although the radiation from specific targeting of radiolabeled antibodies is primarily absorbed by the malignant cells, a substantial contribution to the adjacent normal marrow cells can occur. In patients likely to have marrow or skeletal targeting, prediction of myelotoxicity by conventional blood and body contributions to marrow is substantially improved by the use of radiation dose to marrow estimated from images. In the experience of DeNardo et al. with 131I-Lym-1 in B-cell malignancies, the contribution to myelotoxicity from targeting of marrow malignancy has been evident. Specific marrow targeting was believed to be a major, but variable, factor in the observed myelotoxicity of the patients. Imaging of the distribution of the radiolabeled antibody provided useful clues for estimating the radiation contributed to marrow from targeting (Figure 5). Marrow targeting can contribute marrow radiation that is several times greater than that from the blood and body of the patient. Although prediction of myelotoxicity was improved by the use of targeted radiation dose to marrow, the accuracy of prediction can be further improved by consideration of other factors. Sgouros et al. have published a comprehensive review on red marrow dosimetry.

**TREATMENT STRATEGIES AND METHODS**

Chemotherapy doses are determined based on dose-escalating studies intended to determine the maximum tolerated dose (MTD) of a drug or combination of drugs in small cohorts of patients.
There is little individualization unless conducted on an empiric basis. For some chemotherapeutic drugs, the AUC can be used to prescribe doses of the drug.

Patient-specific calculations of radiation doses are routine in external beam radiotherapy. However, the intended radiation doses are determined by the response-morbidity relationships observed in studies of earlier patients. Treatment planning involves careful definition of radiation dose distribution to optimize response and morbidity for each patient.

In radionuclide therapy, the drug pharmacokinetics and radiation dose distribution can be estimated for an individual patient using a tracer amount of the radiolabeled drug intended for subsequent therapy. Recently, the spatial characteristics of the specific patient and energy distribution of the specific radionuclide have been used to generate patient-specific radiation dosimetry, as described earlier. Treatment planning strategies that provide recommendations for individual patients based upon estimates of radiation dose distribution for each combination of radionuclide and targeting drug have been described.

### Strategies

The strategy for radionuclide therapy can be designed for administration of one or more doses (cycles) of the therapeutic drug. If the treatment plan intends administration of a single dose of therapeutic drug, the amount of radionuclide may be chosen as the MTD for the dose-limiting critical tissue, usually marrow, or for a secondary tissue when bone marrow reconstitution is incorporated. Press et al. have shown an impressive efficacy and safety profile for $^{131}$I-labeled MAb in patients with NHL. Almost a curie of $^{131}$I was administered to patients in a myeloablative strategy. A single dose of $^{131}$I or $^{90}$Y-labeled MAb has also been shown to be remarkably effective in a nonmyeloablative strategy. Contrariwise, radionuclide therapy is often less effective for other cancers so that dose-intensification strategies must be examined. Administration of multiple doses of the drug intended for radionuclide therapy is often referred to as “fractionation,” although it does not entirely fulfill the traditional radiobiologic requirements developed from conventional radiotherapy experience. Importantly, fractionation of radionuclide therapy is a strategy for overcoming nonuniform radiation doses in the cancer that occur because of heterogeneity of drug distribution. Preclinical and clinical data have shown that toxicity can be better controlled, the MTD extended, and efficacy increased by multiple dosing at or near the MTD. If radionuclide dose is selected at the MTD, then an interval must be chosen between doses that permits adequate normal tissue recovery. DeNardo et al. have shown good results for fractionated RIT in patients with NHL, using low doses of $^{131}$I-labeled MAb in 4 or more cycles.

### Dose Prescription Methods

In current trials, there are two commonly used algorithms for prescribing the therapeutic dose of radionuclide (GBq) to be administered to the patient. These can be referred to as fixed and individualized methods. The latter method considers individual variations in drug pharmacokinetics and radiation dosimetry to generate a patient-specific dose of radionuclide. This treatment-planning paradigm, initially proposed by Benua et

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**Figure 5.** Lumbar vertebral images from three representative patients with NHL that had received $^{131}$I-Lym-1 MAb. Images for the patient on the left showed no evidence for marrow targeting, that in the middle showed some evidence, and that on the right showed substantial marrow targeting of $^{131}$I-Lym-1 that added significantly to the marrow radiation dose from nonspecific sources such as the contributions from blood and body activity.
al. for thyroid cancer, requires serial time-activity measurements for critical tissues after administration of a tracer amount of the drug. These data are then used to determine the cumulated activities in the dose-limiting tissues, to estimate the radiation doses, and to determine the therapeutic dose of radionuclide. This approach is important, perhaps even essential, for drugs that have considerable interpatient variability in pharmacokinetic behavior. When experience proves that a radionuclide drug has little interpatient variability in behavior, and that a fixed dose of radionuclide is safe and effective, then a fixed radionuclide dose for patient populations can be considered in order to achieve logistical and economical advantages. To some extent, the basis for decision between these dosing methods is a philosophical one relating to the definition of “optimum dose.” The burden for those espousing radiation dose-based treatment planning is to document better efficacy and/or lesser toxicity for patients treated using this method. The burden for those espousing a fixed radionuclide dose is to show, at the most, that a radiation dose-based method does not improve results, and, at the least, that there was no information, such as pharmacokinetic data, upon which to better select radionuclide dose. In summary, a primary purpose for obtaining radiation dosimetry is to maximize the likelihood of a safe and optimally effective treatment for each patient. Certain situations may require treatment planning for an individual patient whereas others may not. Radiation dosimetry can always be utilized as a tool for assessing results or as a guide to establish the safety of a specific radionuclide drug in the stages of drug development. Myelotoxicity, the major dose-limiting toxicity of radionuclide therapy, presents special difficulties in obtaining clinically meaningful dosimetry estimates. However, myelotoxicity can also be ameliorated by bone marrow reconstitution. As radionuclide doses are escalated without the limitation of bone marrow suppression, toxicity to other organs, such as the lungs and liver, becomes dose-limiting. Thus, normal organ dosimetry becomes critical in the setting of high dose radionuclide therapy.

ACKNOWLEDGMENTS

We wish to express our appreciation for insights gained from fruitful discussions with colleagues through the years. These discussions, and experience using radionuclide therapy in patients, have led to the distillate expressed herein. This research was supported by grants from the National Cancer Institute (PO1-CA47829) and the U.S. Department of Energy (DOE) (DE-FG03-84ER60233). Some of this work was performed under the auspices of the U.S. Department of Energy by the Lawrence Livermore National Laboratory under Contract W-7405-ENG-48. The authors would also like to acknowledge Nona L. Simons for substantial assistance in preparing the manuscript.

REFERENCES

11. Furhang EE, Chiu CS, Sgouros G. A Monte Carlo ap-


58. Richman CM, DeNardo SJ, O’Grady LF, DeNardo GL.