

Red marrow dosimetry for radiolabeled antibodies that bind to marrow, bone, or blood components

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Hematologic toxicity limits the radioactivity that may be administered for radiolabeled antibody therapy. This work examines approaches for obtaining biodistribution data and performing dosimetry when the administered antibody is known to bind to a cellular component of blood, bone, or marrow. Marrow dosimetry in this case is more difficult because the kinetics of antibody clearance from the blood cannot be related to the marrow. Several approaches for obtaining antibody kinetics in the marrow are examined and evaluated. The absorbed fractions and *S* factors that should be used in performing marrow dosimetry are also examined and the effect of including greater anatomical detail is considered. The radiobiology of the red marrow is briefly reviewed. Recommendations for performing marrow dosimetry when the antibody binds to the marrow are provided. © 2000 American Association of Physicists in Medicine. [S0094-2405(00)01009-9]

I. INTRODUCTION

The importance of red marrow toxicity in radiolabeled antibody therapy is well established.^{1–13} In essentially all cases of intravenously administered radioimmunotherapy, the red marrow has limited the amount of radioactivity that may be administered. Even in nonintravenous administrations hematopoietic toxicity has been limiting.^{14–18} A number of diverse approaches have been examined to ameliorate or overcome such toxicity. These approaches include the use of growth factors, marrow rescue, marrow transplantation, immunoadsorption, and multistep targeting techniques that include clearing agents.^{19–43} To date, most marrow exposures have been the result of a single administration of therapeutically labeled antibody. As humanized antibodies become increasingly available,^{44–48} multiadministration protocols, in which several cycles of radiolabeled antibody are administered over a several week to month period, will be implemented.^{25,49–56} Such treatment protocols will introduce new challenges to red marrow dosimetry while also making such dosimetry increasingly important.

The amount of administered radioactivity at which bone marrow toxicity is encountered is usually established with phase I dose escalation studies. The data from such studies have provided general guidelines regarding the potential

marrow toxicities of different radionuclides and different antibody targets. Nevertheless, the relationship between administered activity and marrow toxicity obtained from most phase I dose escalation trials is relevant only to the particular antibody, radiolabel, administration protocol, and patient population that is being considered. This relationship may be generalized by converting administered radioactivity to red marrow absorbed dose. By accounting for the factors that are known to lead to marrow toxicity (e.g., residence time, emission characteristics, localization) absorbed dose is expected to predict potential marrow toxicity. Analyses of the absorbed dose versus hematologic toxicity have confirmed this but have also highlighted the importance of biological factors in predicting toxicity.^{9,57–67}

Ideally, the relationship observed between red marrow absorbed dose and hematopoietic toxicity should be identical for all clinical trials. That is, the maximum tolerated dose, when expressed in terms of absorbed dose to marrow, should be independent of antibody, patient protocol, and radionuclide. In practice, this has not been observed. Three important considerations must be addressed before a definitive correspondence between absorbed dose and marrow toxicity may be made. (1) A clinically implementable, consistent approach to marrow dosimetry must be established for calculating marrow absorbed dose. (2) A measure of marrow ra-

diosensitivity is needed to help translate absorbed dose to normal tissue complication probability. (3) An assessment of each patient's bone marrow reserve is needed. The first item is important because of the wide range of estimates and assumptions that may be made in performing the dose calculation. The second and third items are necessary to overcome the variability in dose response arising from differences in patient treatment history and the resulting differences in marrow susceptibility to radiation.

Significant progress has been made in establishing a consistent approach to marrow dosimetry for antibodies that do not specifically target cellular components of bone, marrow or blood. Following a detailed analysis of the literature, the American Association of Physicists in Medicine (AAPM), Task Group on the Dosimetry of Radiolabeled Antibodies, formulated an approach for estimating red marrow kinetics.¹ In this approach the radioactivity concentration in red marrow is set equal to the concentration in blood multiplied by a factor between 0.2 and 0.4. Recent theoretical and experimental work has narrowed this range to between 0.32 and 0.36.^{2,68} After the blood clearance kinetics are converted to a marrow time-activity curve, the cumulated activity in marrow obtained by integrating over time, along with estimates of total body and other organ cumulated activities may then be used in the Medical Internal Radiation Dose (MIRD) Committee *S* factor schema to estimate marrow absorbed dose.⁶⁹ This approach to obtaining absorbed dose from cumulated activity or residence time in marrow is considered adequate in the absence of specific marrow localization. It is important to note that a direct implementation of the *S*-factor schema requires an estimate of marrow mass. Starting with the mathematical definition of *S* factors, it is possible to derive an expression that incorporates marrow self-dose and total-body marrow dose without the explicit use of marrow mass.⁷⁰ Marrow dosimetry for radiolabeled antibodies or from breakdown products (including free labels) that bind to cellular components of bone, marrow or blood (i.e., actively distributed antibodies) introduce considerably greater complexity. The complexity arises primarily because cell-level considerations become important in predicting toxicity. The potential for selectively irradiating a given population of cells requires a cell-level analysis of the absorbed dose. To perform such an analysis, information is needed on the time-dependent localization of the labeled antibody (or free label). These data, along with knowledge of the geometry of the relevant structures and the decay characteristics of the radionuclide, could then be used to estimate the absorbed dose to the dose-limiting population of marrow cells. Because of the intricate bone-marrow architecture, such calculations need to account for the architecture of bone marrow with respect to cortical and trabecular bone.⁷¹⁻⁷⁷ One must: (1) first identify the population of cells to which the antibody (or label) binds, (2) determine the residence time of the radiolabel on these cells, (3) place these cells within the overall geometry of the bone marrow, (4) determine the dose-limiting population of cells and their position relative to the labeled cells, and (5) then calculate the absorbed dose to these critical cells, (6) ensuring that such calculations properly account for effects at

the interface between bone and soft tissue.⁷⁸⁻⁸⁰ Once the absorbed dose to the relevant cell population has been estimated, information regarding the radiosensitivity of these cells is required to determine the probability of producing significant marrow toxicity with a particular administration of radiolabeled antibody. Last, one needs to know the effects of disease or prior therapy on the physiological bone marrow reserve.

Given these complex factors, accurate patient bone marrow dosimetry for antibodies (or radiolabels) that show specific marrow targeting remains a challenge. Detailed dosimetry for such agents is feasible given patient-specific information such as kinetics (obtained from external imaging) and marrow localization and architecture (obtained from bone marrow core biopsies) combined with previously calculated estimates of the absorbed dose to critical cell populations from a variety of labeled cell types and for a number of different radiolabels. In such an approach, for example, the macroscopic kinetics of a radiolabeled antibody would be extrapolated to the cell level based upon previously established correction factors.

In this work, we bring together the basic information required to develop and clinically implement the above-outlined approach. An overview of the pertinent anatomy is presented in Sec. II. Various techniques for quantitating the macroscopic distribution of radioactivity are discussed and evaluated in Sec. III. In Sec. IV the importance of subdividing the marrow into individual regions for cumulated activity determination is discussed and evaluated relative to measured marrow activity distributions in patients. Potential cell-level source regions are also identified in Sec. IV and the assumptions involved in obtaining cumulated activity estimates for these source regions are evaluated and discussed. On a macroscopic scale, Sec. V discusses the use of *S* factors for individual marrow regions. Section VI examines various approximations for cell-level dosimetry; the impact of bone-tissue interface effects are also discussed in this section. Section VII addresses the radiobiology of red marrow irradiation. A series of specific, clinically implementable, recommendations on how to perform red marrow dosimetry for marrow-binding antibody are presented in Sec. VIII. The accuracy of the red marrow absorbed dose calculations is assessed in Sec. IX.

II. OVERVIEW OF PERTINENT ANATOMY

Bone marrow (BM) is a soft, gelatinous tissue which fills the cavities of the bones. BM can be either red or yellow, depending upon the preponderance of vascular (red) or fatty (yellow) tissue. In humans, the red marrow produces all of the blood cells with the exception of lymphocytes. The vascular supply of bone marrow is derived from a central artery which runs parallel to the long axis of the bone marrow and divides into capillaries. Capillaries run into specialized vascular structures known as sinuses or sinusoids.

The total weight of the red marrow varies with age reaching its peak between 20 and 30 years of age (1120 g for a reference male, 1050 g for a reference female;^{81,82} reference

weight is model dependent—see Sec. V and then declines. Depending upon the anatomical location, RM content, at age 40, has been estimated to range from 0.40 to 0.75 of its peak value in a 70 kg person.⁸³ Total red marrow is distributed as follows: 28.4% in the vertebrae, 26.1% in the lower limb girdle, 13.9% in the sacrum, 13.1% in the head. The remaining 18.5% of the total marrow is in the ribs, upper limb girdle, and sternum.⁸⁴

III. TECHNIQUES FOR QUANTITATING THE RADIOACTIVITY DISTRIBUTION (MACRODISTRIBUTION)

The kinetics of radiolabeled antibodies that actively distribute in the marrow and/or skeleton cannot generally be obtained from blood measurements.¹ The uptake and clearance in marrow or bone must be measured by imaging or sample collection. Due to the potential variability between patients, such measurements must usually be made for each patient and radiopharmaceutical.^{85,86}

A. Marrow aspiration

The fraction of blood in marrow aspirates can range from 0.5% to 96.5%.⁸⁷ Fauci⁸⁸ showed that approximately 70% of a typical aspirate volume was peripheral blood. This constitutes a large quantitative uncertainty when there is a large concentration of antibody in the blood with respect to a small amount of radiolabeled antibody in the red marrow extravascular space.⁸⁹ Although it is possible, in principle, to correct marrow aspirate radionuclide concentrations for contamination, this correction requires a second tracer that remains in the vascular space, such as labeled red cells.⁸⁷ However, *in situ* radionuclide concentrations may not be accurately measured even with this correction.⁹⁰

B. Marrow biopsy

Biopsies are much more representative of marrow contents and they measure radionuclide that may localize to bone, such as Y-90. They are also useful for quantitating marrow activity for radionuclides without gamma emission suitable for imaging. Biopsy samples are, however, subject to sampling and processing uncertainties. Although iliac crest biopsies have been shown to be representative of whole-body red marrow in autopsy cases with nonhematologic and nonosseous disorders,⁹¹ the same has not been demonstrated for radiolabeled antibody distribution in cancer patients. On the contrary, leukemia patients exhibit a variable distribution of radioactivity following antibody administration.^{86,92} In addition to the potential sampling error, the marrow activity concentration determined from a biopsy is also subject to errors associated with sample preparation prior to counting. These errors arise because a core biopsy also includes trabecular and cortical bone, fatty tissue, and blood. Depending upon the distribution of the antibody, these may over- or underestimate the true marrow activity concentration if sampling variables are not accounted for in determining the activity concentration.²

The pain and discomfort associated with obtaining marrow biopsies severely limits the number of samples that can be obtained from a single patient and, consequently, their utility for assessing marrow activity concentration over time. The direct activity concentration obtained from biopsies must, therefore, be combined with additional data regarding kinetics to generate a complete marrow time-activity curve.

C. Imaging

If the radiolabel emits photons appropriate for external gamma camera imaging, imaging may be used to obtain marrow kinetics. This information may then be combined with one or more marrow biopsies to transform the resulting time-activity curve to absolute activity concentration in marrow over time.⁹³

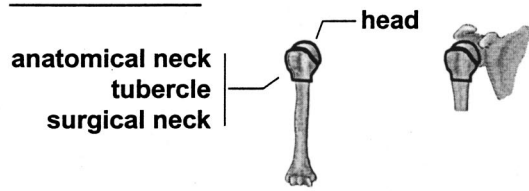
Marrow kinetics from imaging are usually obtained by drawing a contour around a marrow-rich region on each of a series of planar images collected over time.^{86,94–97} Several marrow-rich regions have been used for this purpose, including the head and neck of the femur, the head of the humerus, lumbar vertebrae 3 and 4, and the sacrum; adjacent regions that are not over major vessels or activity-concentrating organs (e.g., kidney, liver or spleen) have been used for background estimation. Figure 1 depicts the contours drawn for the marrow regions.

The kinetics obtained from the femoral, humeral, and lumbar regions have been intercompared in a series of leukemia patients receiving HuM195 (anti-CD33) antibody radiolabeled with tracer amounts of ¹³¹I.⁸⁶ A greater than two-fold variability was observed both between different regions in a given patient and amongst different patients for a particular region. This variability was observed in both the radioactivity concentration and clearance half-time. In leukemia patients, this may arise primarily because the target cells are not uniformly distributed within the marrow. Nonuniform antibody distribution and clearance kinetics make it difficult to predict the relationship between the mean absorbed dose to marrow and the probability of ablating the marrow. This variability may lead to over- or underestimates of the absorbed dose to marrow. As expected for an antibody that specifically binds to marrow, the blood clearance half-times for each patient in the study were consistently lower than that of the marrow.

The localization and activity concentration in marrow may be determined using positron emission tomography (PET).^{98–103} Using the positron emitter, iodine-124, quantitative data directly relevant to radiolabeled antibody therapy with ¹³¹I may be obtained. To address the issue of marrow localization, Kwok *et al.*⁶⁸ have used ¹¹CO-labeled red blood cells and ⁶⁴Cu-labeled nonspecific human IgG to measure, by PET, the exchange rates of the IgG between bone marrow and parenchyma and the blood compartment of a lumbar vertebra in adult dogs. PET quantitation of antibodies in tumors and different organs in humans have also been reported,^{99,100} no measurements have been reported for marrow in patients with marrow involvement.

Marrow Region-of-Interest Anatomy

Humerus:



Femur:

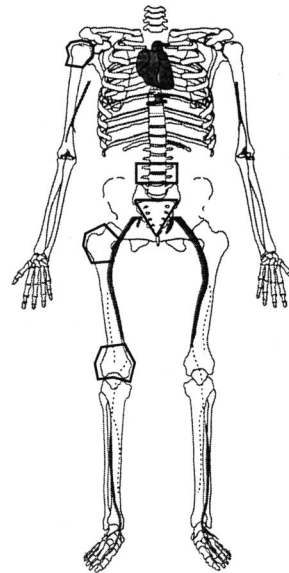
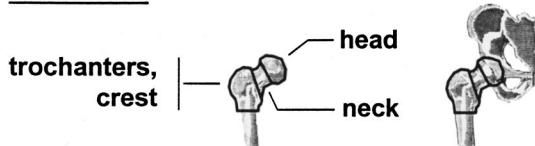


FIG. 1. The regions of interest (ROI) that are typically used to obtain marrow pharmacokinetics from planar imaging studies are depicted on the right-hand side. The rectangular ROI is drawn around lumbar vertebra 3 and 4. The triangular ROI is drawn around the sacral area. The humeral and femoral regions are expanded on the left-hand side to indicate the specific anatomical regions.

IV. APPORTIONMENT OF THE MACRODISTRIBUTION (MICRODISTRIBUTION)

Figure 2 depicts the various anatomical and functional volumes to which marrow radioactivity may be apportioned. The first level, “bone marrow,” represents information obtained from imaging or from an unprocessed core biopsy.

A. Bone

If the biopsy sample is processed so that the bone is isolated from the marrow and each is counted separately, a secondary level of information regarding bone localization of a particular radionuclide-antibody combination may be obtained. Such information may be critical for radionuclides that localize to bone following detachment from the antibody (e.g., Y-90). A further distinction may be made between cortical and trabecular localization by separating the cortical bone “cap” from trabecular bone in a bone marrow biopsy and counting these separately. Since radioactivity in cortical bone irradiates a smaller fraction of the marrow than a comparable source in trabecular bone, knowledge of the apportionment is important in estimating the dose to red marrow. A further subdivision between surface and volume is also shown in Fig. 2. This subdivision applies to both cortical and

trabecular bone. Bone surface corresponds to the first 10 μm layer of endosteal cells adjacent to the bone matrix itself.⁷¹ Such information is generally obtained by autoradiography or by *a priori* knowledge of a particular agent’s localizing pattern in bone.¹⁰³ Further detail regarding the localization of a radionuclide (e.g., in osteoblasts/osteoclasts, matrix, or mineral) becomes important primarily for the quantitative assessment of the risk of radiation-induced malignant transformation.

B. Red marrow

Detailed assessment of antibody and radionuclide localization in bone-free samples of red (cellular) and yellow (fatty) marrow is significantly more difficult both because a biopsy does not preserve the extravascular and vascular architecture of marrow and because the radioactivity concentration in each of these compartments is subject to a more rapid change over time than in the bone compartments. In red marrow, the primary sites of antibody localization are within the extracellular fluid space, the vasculature, and the hematopoietic tissue itself. Antibody or its radiolabel may localize to red marrow either by interacting with one or more

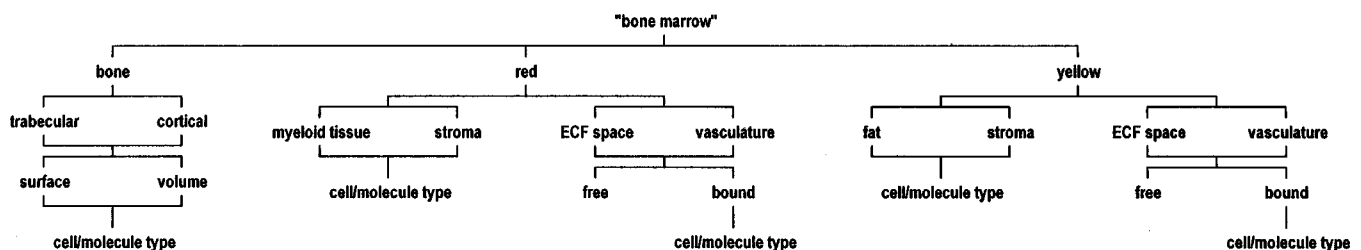


FIG. 2. Hierarchy of bone marrow functional and anatomical spaces.

of the hematopoietic cell lines, by binding to tumor cells that have infiltrated the marrow extracellular fluid or vascular space, and by reacting directly with myeloid tissue.

A distinction between the vasculature and the trabecular, marrow-containing, cavities is necessary since the geometries differ significantly. The dimensions of marrow cavities have been examined in detail and have been summarized as a distribution of chord lengths for various red-marrow containing trabecular regions.^{104–107} No such simplification has been developed for the vasculature. The distinction may be important since trabecular cavities will have a different density of cells compared to the vascular lumen. The difference in cell density will depend upon the type of cell. Precursor or stem cells, for example, will be much more highly concentrated in the marrow cavities than fully differentiated mature cells. In contrast, marrow-infiltrating tumor cells may be more concentrated in the vasculature than in the cavities, since they may be assumed to originate outside of the marrow. Although such detailed information regarding the concentration of different cells in different regions of the marrow is not easily available, formulation of the problem in this way can help guide the collection of dosimetrically useful data especially in the case of an antibody which is known to cross-react with a particular class of cells.

As indicated in Fig. 2, free or unbound antibody is also expected to contribute to the red marrow dose. Since the capillary basal lamina of marrow is incompletely developed, rapid equilibration of antibody between plasma and the extracellular fluid space of marrow may be assumed. The concentration of antibody in the vascular and extracellular fluid space of marrow can, therefore, be equated with that in the plasma. This approach, essentially corresponds to the approach used for marrow dosimetry when the antibody does not localize to marrow.²

C. Yellow marrow

Significant localization of antibody to yellow marrow has not been observed and would be of little consequence since hematopoietic toxicity has not been associated with irradiation of yellow marrow. It is important to note, however, that when the red or active marrow has been significantly compromised, regions that ordinarily contain yellow marrow may be converted to red marrow. In this regard, the stroma in the yellow marrow may be considered a reserve and radiation-induced damage to yellow marrow (stroma) may diminish its capability to facilitate marrow expansion. The volume of yellow marrow would also impact upon dose delivery to red marrow and potential toxicity by reducing the initial distribution of the antibody and, therefore, increasing the activity concentration to which the marrow is exposed.

V. S FACTORS

Red marrow *S* factors (also referred to as dose conversion factors or *S*-values) have been difficult to estimate due to the nature of trabecular bone geometry and the general difficulty in evaluating absorbed dose in this irregular structure. Spiers and co-workers provided much material in the literature, pri-

marily dealing with the evaluation of absorbed dose to the marrow from electron and beta emitters in the volume of mineral bone.^{104–106} Much of this information was incorporated by the MIRDC Committee into their dose conversion factors (*S* values) published in MIRDC Pamphlet 11.¹⁰⁸ This document also incorporated specific absorbed fractions (SAFs) for photons based on the work of Snyder and co-workers using the 70 kg adult phantom, in which the skeleton was represented as a homogeneous mixture of bone and marrow. The SAFs employed in this document for bone irradiating marrow were known to be conservatively high for photons below about 300 keV, as stated by the authors themselves.

Cristy and Eckerman later published photon SAFs for a series of phantoms ranging in mass from 3.4 to 70 kg and representing individuals of different ages ranging from newborns to adults.^{81,82} In their work, an improvement was incorporated into the low energy photon dosimetry to correct for the problem in Snyder *et al.*¹⁰⁹ and in the *S* values of MIRDC Pamphlet 11. The improvement introduced by Cristy and Eckerman involved the modeling of energy deposition by secondary electrons liberated by photon interactions in the skeleton. The International Commission on Radiological Protection (ICRP), in ICRP Publication 30,¹¹⁰ made limited use of the data of Spiers and co-workers, and employed photon SAFs from ICRP Publication 23,⁸³ in developing dosimetry for a number of radionuclides within the framework of a system of radiation protection for workers.

Eckerman¹¹¹ recalculated the values of Spiers and co-workers, in order to establish the absorbed fractions for electrons for most bone groups across a wide range of energies and to combine them with the newer photon SAFs. The seven bone types identified by Spiers *et al.* (Table I) were combined with various assumed fractional abundances of each bone type ($n=7$) within the bone regions ($n=15$) of the Cristy–Eckerman phantom series. This work was presented at the Society of Nuclear Medicine meeting in June, 1994.¹¹² A description of a generalized dosimetry software package using these values has been published.¹¹³ A sample of the factors within the model which assign fractions of the bone and marrow components to different regions of the skeleton and the factors which relate bone types to bone regions is shown in Table I. This model allows calculation of absorbed dose to the marrow by marrow region. This new model for marrow dosimetry has the potential for more accurately predicting observed marrow toxicity, both because of the improvements to the photon and electron dosimetry and because of the ability to study marrow dose by region and by fractional volume. An average marrow dose can be obtained with the Eckerman model by weighting the marrow doses in the different regions by the fraction of marrow in each region and by the cellularity. A comparison of the mean marrow doses predicted by this model with values predicted by the marrow models used in MIRDC 11 and ICRP 30 is given in Table II. The new model gives essentially the same results as MIRDC 11, although the new model *S* values are consistently a little lower. The new model results, however, are considerably lower than those predicted by the ICRP 30

TABLE I. Assigned cellularity factors (cf) and fractions of different bone components in the 15 bone regions of the adult phantom.

Skeletal region ^a	CF	Ftrab	Fmar	Ftbs	Fcort	Fcbs	Bone groups ^b			
Legs upper...	0.250	0.163	0.033	0.167	0.140	0.084	0.8	FH	0.2	FN
Legs middle...	0.000	0.165	0.000	0.169	0.207	0.113	0.5	FH	0.5	FN
Legs lower...	0.000	0.040	0.000	0.040	0.082	0.107	0.5	FH	0.5	FN
Arm upper...	0.250	0.030	0.023	0.031	0.070	0.032	0.8	FH	0.2	FN
Arm middle...	0.000	0.025	0.000	0.026	0.047	0.024	0.5	FH	0.5	FN
Arm lower...	0.000	0.026	0.000	0.026	0.044	0.032	0.5	FH	0.5	FN
Pelvis...	0.580	0.018	0.333	0.018	0.014	0.073	0.6	IC	0.4	LV
Spine upper...	0.720	0.107	0.027	0.110	0.009	0.012	1.0	CV		
Spine middle...	0.720	0.276	0.174	0.282	0.024	0.045	0.5	CV	0.5	LV
Spine lower...	0.720	0.069	0.098	0.071	0.008	0.019	1.0	LV		
Skull cranium	0.420	0.026	0.056	0.012	0.128	0.042	1.0	PB		
Skull Facial...	0.420	0.013	0.028	0.006	0.063	0.020	1.0	PB		
Ribs...	0.720	0.030	0.192	0.031	0.120	0.048	1.0	RB		
Clavicles...	0.370	0.002	0.008	0.002	0.009	0.004	0.6	IC	0.4	LV
Scapulae...	0.420	0.009	0.028	0.009	0.036	0.014	0.6	IC	0.4	LV

^aAbbreviation for skeletal regions: CF=cell fraction; Ftrab=trabecular bone fraction; Fmar=active marrow fraction; Ftbs=trabecular bone surface fraction; Fcort=cortical bone fraction; Fcbs=cortical bone surface fraction.

^bThe major bone groups defined in the Spiers bone marrow model are listed, the abbreviations are: FH, FN=femur head, neck; IC=iliac crest, LV=lumbar vertebrae, CV=cervical vertebrae, PB=parietal bone, RB=rib.

model. It should be remembered that the ICRP model was quite conservative, as the intent of the model was to provide a system of radiation protection for workers, not an accurate model for clinical radioimmunotherapy. Its results for doses around the 50 mGy level are probably adequate, but not useful for marrow dosimetry in radionuclide therapy.

In general, the model of Eckerman is an improvement on the older MIRD and ICRP models, as the low energy photon dosimetry and the electron dosimetry have been updated and improved.¹¹¹ Table III summarizes the characteristics of each of the models.

VI. MULTICELLULAR ABSORBED FRACTIONS

Localization of the radiolabeled antibody and the radionuclide within the red marrow and bone will dictate the level of detail required for multicellular absorbed dose calculations. In the following, three different assumptions are considered: (1) bone or marrow parenchyma as source, activity uniformly distributed within each; (2) assumption (1), but with the incorporation of interface effects between bone and soft tissue; (3) compartments within the cell are identified as sources, kinetic data for subcellular compartments are inte-

grated, over time, and combined with cell-level S factors^{73,114} to estimate the absorbed dose to the cell nucleus.

A. First approximation

In the first approximation, the marrow parenchyma and the trabecular bone are separately regarded as source regions. The concentrations of radiolabeled antibody in the two regions are assumed uniform but not identical. Bone/soft tissue interface effects are ignored.

The absorbed fraction, ϕ , for alpha particles in the marrow parenchyma can be taken as one because the mean ray length for marrow cavities of the vertebrae and the iliac crest of adults is greater than 700 μm .¹⁰⁵⁻¹⁰⁷ This is considerably greater than the 40–80 μm soft tissue range of alpha particles used in radioimmunotherapy. Under the assumption of uniform deposition in bone, irradiation of the red marrow by alpha particle emitters within bone will be negligible. The absorbed fraction for beta particles in the parenchyma or the trabeculae may be less than one, depending on the energy spectrum of the source. Eckerman¹¹¹ has tabulated ϕ as a function of electron energy. The mean value of ϕ for a beta source can then be obtained by integrating the monoenergetic ϕ values with the emission spectrum of the source. Shearer *et al.*¹¹⁵ have also calculated ϕ for several beta-emitting nuclides uniformly distributed in various bone types. Spherical marrow cavities were assumed for the trabecular bone. A ϕ value of 0.79 for ¹³¹I uniformly distributed in trabecular marrow was derived by McEwan *et al.*¹¹⁶ from the beta ray dose factors of Whitwell and Spiers.¹¹⁷

The absorbed fraction for uniformly distributed gamma-emitting sources in small unit-density spheres or ellipsoids is given by Ellett and Humes¹¹⁸ as a function of photon energy and mass of the object. Each of the objects is assumed surrounded by an infinite medium of the same materials. This does not simulate trabecular bone well for low to medium

TABLE II. Comparison of skeletal average S values active marrow as a source and target.

Radionuclide	$S(RM \leftarrow RM)$ (mGy/MBq)		
	MIRD 11	ICRP 30	Eckerman model
H-3	6.1×10^{-7}	8.3×10^{-7}	5.0×10^{-7}
C-14	5.0×10^{-6}	7.1×10^{-6}	4.1×10^{-6}
Fe-59	1.5×10^{-5}	2.1×10^{-5}	8.7×10^{-6}
I-131	1.7×10^{-5}	2.8×10^{-5}	1.4×10^{-5}
Sm-153	2.3×10^{-5}	3.8×10^{-5}	1.9×10^{-5}
P-32	4.9×10^{-5}	9.8×10^{-5}	4.4×10^{-5}
Y-90	6.5×10^{-5}	1.4×10^{-4}	5.9×10^{-5}

TABLE III. Description and characterization of different marrow *S* factors.

MIRD 11	ICRP-30	Eckerman model	
Source	MIRD, Pamphlet No. 11	MIRDOSE 2	MIRDOSE 3
Technical basis	Spiers' electron dosimetry, MIRD five photon dosimetry	ICRP 30 electron dosimetry, Cristy/Eckerman photon dosimetry	Eckerman electron dosimetry, Cristy/Eckerman photon dosimetry
Major characteristics	Energy-dependent electron and photon dosimetry, target tissues red marrow and "bone," limited accuracy of photon dosimetry below 300 keV	Little or no energy dependence of electron dosimetry, improved low energy photon dosimetry	Improved energy dependent electron and photon dosimetry
Red marrow Mass	Male adult=1500 g Female adult=1180 g	Male adult=1120 g Female adult=1050 g	Male adult=1120 g Female adult=1050 g

energy photons (<50 100 keV). Nevertheless, for gamma-emitting nuclides, uniformly distributed in the marrow parenchyma or in trabecular bone, these tabulated ϕ values are appropriate.

B. Second approximation incorporating bone/soft-tissue interface effects

Using Monte Carlo techniques and assuming that marrow cavities may be represented as 500 μm radius spheres, Kwok *et al.*^{78,79,119} estimated the maximum dose increase within 20 μm of the trabecular bone/bone marrow interface. An isotropic distribution of monoenergetic electrons inside the cavity yielded a dose increase of $21 \pm 1\%$ for 0.5 MeV electrons. The dose increase, averaged over the whole sphere, was $12 \pm 0.6\%$. Such estimates should be regarded as upper limits because the thickness of trabeculae used in the calculations was greater than that required to saturate the backscatter dose. The average dose increases for ^{131}I and ^{90}Y , uniformly distributed in the 500 μm radius spheres, were 5% and 4%, respectively. The average dose increases for the same nuclides in 300 μm radius spheres were 6% and 4%, respectively. This suggests that the average dose increase due to electron backscatter from the trabecular bone is not sensitive to the size of the marrow cavity.

Variations with photon energy in the ratio of absorbed dose in active marrow to the equilibrium dose in soft tissue were given by Eckerman.¹¹¹ These ratios are maximal at photon energies in the region of 50–60 keV and are higher for the thick trabeculae and small marrow cavities of the parietal bone than for the thinner trabeculae—larger marrow cavities—of other bones. Maximum enhancement for most trabecular sites is approximately 15%.

Enhancement of absorbed dose in active marrow due to backscattering of alpha particles from trabecular bone is negligible because of the relatively low atomic number of bone.

C. Third approximation incorporating intracellular localization

A cellular apportionment of the radiolabeled antibody is warranted if the radionuclide emissions travel distances that fall within cellular dimensions and the antibody or radionuclide are known to internalize or otherwise distribute preferentially within the cellular geometry. This is the case for antibodies labeled with Auger or conversion electron emitters.^{120–126} In these cases the macroscopic absorbed dose should be modified so that the absorbed dose to the cell nucleus is considered rather than the mean dose over a tissue volume. If the fraction of cumulated activity that is cytosolic versus nuclear versus membrane-bound can be estimated, then previously published *S* factors may be used to obtain the absorbed dose to the nucleus.¹²⁷ Such calculations are relevant only if the number of decays in each compartment and correspondingly the number of hits to the chosen target are sufficient so as to be outside of the microdosimetric or stochastic regime.¹²⁸

VII. RADIOBIOLOGICAL ISSUES

The accurate calculation of absorbed dose to bone marrow elements is quite complex due to the heterogeneous nature of the uptake of radiolabel as well as the relative physical locations of the source and target structures. The relation of this calculated absorbed dose to radiobiological effect might be even more problematic to quantitate with the ultimate expectation of predicting clinical outcome. Nevertheless, the basic response of bone marrow to irradiation is still governed by the classical four "R's" of radiobiology, namely; repair of sublethally damaged cellular components, repopulation of those viable cells, reassortment of cellular cycle, and reoxygenation of hypoxic regions.¹²⁹ The shoulder or initial plateau seen on a plot of the surviving fraction of cells versus the absorbed dose delivered (i.e., cell survival curve) is of particular radiobiological interest for the bone marrow. The high radiosensitivity of bone marrow is evidenced by a small

shoulder on its survival curve with a steep initial negative slope (high α component) followed by a steep terminal slope (β component). A high α/β ratio is characteristic of bone marrow cell survival curves.¹³⁰ Other normal tissues tend to have larger survival curve shoulders, with more repair capacity and high dose-rate dependence, yielding lower α/β ratios.

In radionuclide therapy a significant component of the absorbed dose is from exponentially decaying low dose-rate radiation. This low dose-rate radiation has the effect of enhancing the repair capacity of those tissues which have a relatively large shoulder or low alpha/beta ratio without providing a similar sparing effect to the bone marrow. In addition to its diminished repair capability, the bone marrow also exhibits a high radiosensitivity. On average, the radiosensitivity for bone marrow under similar dose rate conditions is perhaps 10–20 times more sensitive than that of other organs or of tumors (i.e., 30 fractions \times 2 Gy per fraction for breast carcinoma versus 3 fraction of 2 Gy for bone marrow to achieve similar log cell kill).

Although the rapid proliferation rate of marrow leads to the above-described relative susceptibility to low dose-rate irradiation, depending upon the conditions, the rapid rate of proliferation may also provide a survival advantage due to marrow repopulation. There is experimental evidence in animals^{131–135} and humans¹³⁶ to suggest that multiple infusions of radiolabeled antibody, separated by several days to more than a week, may increase the therapeutic index of the treatment relative to a single administration. Analyses of radioimmunotherapy using linear quadratic or time dose fractionation models have been reported.^{137,138}

Since the bone marrow is a distributed organ it is likely that not all areas of bone marrow will be equally accessible to blood-borne antibody. Such nonuniform irradiation is likely to be partially responsible for the diversity in radiobiological response. In solid tissues, such nonuniform irradiation is easily represented using dose-volume histograms, in which the fraction of organ volume receiving a particular absorbed dose is plotted against absorbed dose. This information, in conjunction with a biological model, may then be used to estimate normal tissue complications probability. The concept of normal tissue complications probability, which was popularized by Emami and co-workers¹³⁹ and shown more recently relative to external beam therapy for the liver,¹⁴⁰ provides an interesting approach that may assist in translating the nonuniform marrow absorbed dose into a biological effect. As indicated previously, *S* factors for a number of marrow regions are now available. Combined with regional estimates of radioactivity concentration, dose volume histograms (DVHs) for bone marrow may be obtained. Using a biological model, DVHs, may, in turn, be transformed to normal tissue complications probabilities. It is important to point out that the biological models that may be used for this purpose are still under considerable study in the external beam radiotherapy community and may not necessarily provide estimates of organ complications probability that can be transferred directly to clinical response. This may be the case especially in radioimmunotherapy since there are so many other variables that may influence biological re-

sponse aside from the absorbed dose. Such models may be particularly useful, however, in providing a framework for comparison of different radioimmunotherapeutic approaches.

Perhaps the most important confounding variable in assessing the relationship between marrow absorbed dose and toxicity is that of prior radiation or chemotherapy. Some assessment of bone marrow status or reserve prior to treatment will be essential in high dose protocols that do not include a bone marrow transplant component. Efforts at correlating computed bone marrow dose with observed toxicity either based on percent platelet count at the time of nadir or toxicity grade must be further refined to include pretreatment status of the bone marrow as well as the timing and intensity of the previous chemotherapy or radiation insult.^{57,60–67}

VIII. RECOMMENDATIONS FOR CLINICAL IMPLEMENTATION

A balance between the financial and logistical realities of therapeutic internal emitter studies and the potential morbidity associated with foregoing certain procedures must be struck in formulating a series of clinically implementable recommendations for red marrow dosimetry. In reviewing these recommendations, the distinction between obtaining basic scientific data and obtaining the information required to assess the potential morbidity from a new agent must be preserved. The recommendations correspond to the *minimum requirements* for the latter objective.

A. Basic red marrow localization studies

This section provides recommendations regarding the collection of data that would provide basic information on the distribution of a new agent in the marrow. It is important to emphasize that the recommendations in this section apply to completely new radionuclides or agents which appear to localize in marrow in animal studies but whose distribution within the marrow is unknown. The primary objective of such studies should be to assess the relative distribution of the agent between red marrow and bone. The nature of the localizing agent should also be assessed to determine whether it is the free radionuclide or the intact or metabolized labeled antibody. The need for more detailed information should be determined by the toxicity observed in animal studies. If, after accounting for the general localization of the agent in marrow, unexpectedly high levels of toxicity are observed in animal studies, then more detailed information on the specific localization within bone or marrow and the kinetics in various regions should be obtained. The recommendations for preclinical investigations are summarized in the following.

- (1) Perform animal studies to assess marrow localization.
 - (a) Is it specific? What fraction goes to marrow?
 - (b) Is it to bone or to a cellular component of the red marrow?
 - (c) Is localization predominantly by the agent, by its metabolites, or by the free radionuclide?
- (2) Perform toxicity studies in animals.

- (a) Is the toxicity qualitatively consistent with the observations in item 1(b) above?
- (b) If it is greater, make a hypothesis as to the possible reason and test it by collecting additional data (e.g., cross reactivity with a particularly vulnerable class of cells; internalization with prolonged retention of the radionuclide, etc.).

Typically, items (1) and (2) are satisfied in the initial characterization of a new class of radiolabeled agents and prior to formulating a specific clinical protocol. Notable in its omission is the specific recommendation for red marrow dosimetry based upon the animal data. Although such information is certainly valuable in formulating an optimal strategy for clinical trials and also in helping to establish dose-response relationships that would be of value for future studies, it does not fit within the minimum requirements for assessing a new agent's potential toxicity. Such information is obtained directly from patient, phase I, toxicity studies. In carrying out steps (1) and (2), it is important to recognize that the biodistribution in animals may not always accurately reflect the distribution in humans. This may be particularly true for humanized antibodies and other genetically engineered constructs. In such cases, one must, additionally, rely on theoretical analyses, tracer studies, and characterization, *in vitro* or *ex vivo*, to obtain a preliminary estimate of the starting dose level for a pilot or phase I clinical trial.

B. Protocol-specific red marrow localization/dosimetry studies

In this section, we describe a consistent approach to estimating red marrow absorbed dose in individual patients. Here again, a distinction must be made between obtaining information that will help characterize the potential toxicity of an agent as implemented in a particular protocol and recommendations for the proper estimation of red marrow absorbed dose. The former is obtained directly during the execution of a phase I study. The recommendations that are outlined apply primarily to antibodies labeled with radionuclides that emit photons appropriate for scintigraphic imaging. Four basic issues are addressed: imaging and quantitation, volume determination, biopsy collection, and *S*-factor dosimetry.

1. Planar imaging

No fewer than three, and ideally four, images collected at different times postantibody administration should be obtained. Optimum data collection times would correspond to the collection of one point early in the kinetics of the agent, two intermediate points, and one late point. These time points should be based upon the effective half-life of the radiolabeled antibody in humans. Pharmacokinetic information for the red marrow may be obtained by drawing contours around marrow-rich, low-background regions. Image quantitation may be reduced to three basic elements.

a. Scatter correction A number of scatter correction techniques have been described.¹⁴¹⁻¹⁵² To meet the requirement that scatter correction be simple and clinically implement-

able, energy window-based corrections are recommended. Methods described that allow for scatter correction using two energy windows include: (a) the Compton window methodology of Jaszczak *et al.*¹⁴⁸ with modifications by Koral *et al.*¹⁵³; (b) the dual-photopeak window method¹³⁹; and (c) the channel ratio method.¹⁵² Each of these methods is briefly described in the following

(a) *Compton window*. This method requires that a second ("scatter") energy window be activated during image collection. This window should be the same width as the photopeak window and should be placed below and immediately adjacent to the photopeak window. Images are collected for both energy windows. The lower energy or "scatter window" should be multiplied by 0.5 and should be subtracted from the photopeak window. The scatter window subtraction fraction of 0.5 is an approximation. Ideally, this factor should be determined from phantom studies with and without scattering medium and for different count distributions. The original images (prior to subtraction) should be saved, along with the processed images.

(b) *Dual-photopeak window*. This method is based on the observation that the asymmetry seen in a photopeak is partially the result of scatter. Since the energy of scattered photons is less than the photopeak energy, scattered photons contribute preferentially to the low-energy portion of the photopeak. If the photopeak is divided into two equal (in absolute width), nonoverlapping energy windows a linear relation should be obtainable between the ratio of counts and the scatter fraction. Given such a relationship it is possible to use the ratio of counts obtained from the two photopeak windows to derive an expression for scatter correction.

(c) *Channel ratio*. The channel ratio method is founded on the same principles described previously for method (b), the algorithms implemented for carrying out the correction, however, are different, as are the phantom studies required to obtain the necessary parameters.

Proper implementation of each of these methods requires the determination of one or more parameters that must be obtained by phantom studies or by Monte Carlo methods. The major shortcoming of method (a) is that its accuracy will depend upon the degree to which the activity distribution used for estimating the scatter window subtraction fraction corresponds to the activity distribution obtained in patients. Methods (b) and (c) do not suffer from this shortcoming and have been shown to provide a (marginally) better correction.¹⁴³ Use of these methods, however, requires accurate positioning of the two windows used to span the photopeak so that the photopeak apex is evenly divided between the upper and lower windows.

Inappropriate positioning of these two windows will reduce the accuracy of the scatter correction, and much more important, may compromise the collection of patient data. In light of these considerations, method (a) is recommended because it is simpler to implement, yields adequate results, yet is less subject to errors in energy window placement. It is important to note that considerably more sophisticated methods exist for scatter correction.¹⁴² We describe here three approaches that require as minimal an effort as possible

while yielding results that are better than those without a scatter correction.

b. Attenuation correction. Once a scatter correction has been made, the well-known conjugate-view methodology is recommended for attenuation correction.¹⁵⁴ This technique requires the collection of anterior and posterior planar images. Contours are drawn around a region-of-interest in each view. The square root of the product of the counts obtained from each view yield the “conjugate-view” counts. Although this methodology also typically requires the acquisition of a transmission study, this is not included in the minimum recommendations that we describe here. In most cases of I-131 image quantitation, transmission studies are not collected using I-131 as the flood source because of the difficulty and potential radiation hazard associated with generating a uniform field source of I-131. An alternative radionuclide, such as Co-57, is typically employed and the results are adjusted to account for the difference in attenuation coefficients. Instead of a transmission study, we recommend an analytical correction for attenuation which requires measurement of patient thickness. The thickness, L , is used in the equation, $\exp(\mu \times L/2)$. This expression provides an estimate of the attenuation correction factor for the conjugate-view counts. The value of μ , the photon attenuation coefficient, will depend upon the photon spectrum emitted by the radionuclide and the source geometry. This coefficient is typically obtained assuming a narrow beam geometry and will not exactly represent the value of a distributed source *in vivo*. In the absence of other details, this is a justifiable approach to attenuation correction. Greater accuracy may be obtained if the attenuation correction factor is explicitly measured for a particular source-collimator geometry configuration using a phantom study. Still greater accuracy may be obtained if a CT study is available from which tissue, bone, and air thickness may be obtained. This information may then be used to calculate an effective attenuation coefficient. It is important to note that the above-outlined recommendations represent a minimum effort required to correct for attenuation. Alternative and possibly more accurate approaches exist.^{155,156} The effects of partial volume, as well as under- or overlying activity are not specifically considered as the emphasis is placed on selecting a marrow-rich, low-background region. Quantitative imaging techniques for radioimmunotherapy are provided in greater detail in Ref. 157.

c. Calibration. To convert scatter- and attenuation-corrected counts in a region-of-interest to activity concentration we recommend the use of a calibration standard. The standard should be a distributed source of a known amount of radioactivity that is placed within the camera’s field of view but outside the patient’s body contour. Alternatively, an image of the standard should be collected before or immediately after patient imaging.

2. Volume estimation

An appropriate estimate of the target volume is critical for assessing absorbed dose. Such estimates are particularly dif-

ficult for a distributed organ such as the red marrow. Volume estimates for localized tumors or organs are generally based upon CT or SPECT imaging. These modalities are not as applicable for estimating marrow volume. MRI may provide better estimates of the marrow cavity in a particular region but will not provide information to distinguish between yellow and red marrow. The combination of MRI and spectroscopy may be useful for this purpose.¹⁵⁸ Much greater justification is required, however, before such detailed and costly analysis is recommended. Instead, we recommended that “Reference Man” volume estimates of the red marrow in individual bone regions be used after scaling according to patient weight.⁸³ The volumes corresponding to several marrow-rich, low-background regions are listed which may correspond to contours that can be drawn on planar studies. Total red marrow volume may be obtained by scaling the reference red marrow volume according to patient weight. Such scaling should be performed using a modified or “lean” body weight for obese patients.¹⁵⁹

3. Bone marrow biopsy

If a bone marrow biopsy is obtained it may be used to estimate the radioactivity concentration in marrow. In addition to marrow, a core biopsy typically includes a cortical bone “cap,” trabecular bone, and blood. Assuming that there is not specific uptake in bone, the first two exclude radioactivity and will therefore lead to an underestimate of the radioactivity concentration in marrow while blood may lead to an overestimate.² The bone marrow sample should, therefore, either be processed so as to remove bone and blood contamination before weighing and counting or it should be corrected for the expected effects of such contamination. If bone uptake is observed, cortical and trabecular bone should be counted separately to determine the relative distribution of the radioactivity. Once the red marrow activity concentration has been obtained from a biopsy, it may be used to either check the imaging-based activity concentration estimate or to set its value and then rely on imaging only for the kinetics. In using biopsies for deriving marrow activity concentration, it is important to note that biopsy samples represent a very small fraction of red marrow volume and, therefore, results are highly subject to sampling uncertainties.

4. Absorbed dose calculation

The S -factor based approach that has been described by the MIRD Committee is recommended for red marrow dosimetry.⁶⁹ This approach requires estimation of the cumulated activity or residence time within the red marrow and a set of appropriate S factors.^{109,113} Once a red marrow time-activity curve has been obtained (e.g., using the techniques described previously), it should be integrated over time to yield cumulated activity. If bone uptake has been observed, a separate estimate of the cumulated activity in cortical and trabecular bone should also be obtained when biopsy information is sufficient. If bone uptake has been observed, the dose to the red marrow should then be obtained by consid-

ering at least four source terms: red marrow, the remainder of the body, cortical bone, and trabecular bone. If bone uptake is not seen, the latter two terms will be zero. The contribution to marrow from each source may be obtained using the software package MIRDOSE 3.¹¹³

IX. ACCURACY OF CALCULATIONS

Given all of the issues that have been examined previously, a quantitative assessment of accuracy in red marrow dosimetry for agents that bind to marrow components is complex and subject to random and systematic uncertainties. Since red marrow dose is intended to serve as a measure of potential biologic effect, we are ultimately interested in its accuracy as a biologic index. The difficulty of assessing accuracy is therefore compounded by the challenge of accounting for prior chemotherapy and the resulting change in radiosensitivity and marrow reserve. Given these factors, absorbed dose is one component of the information required to predict marrow toxicity for a particular patient; biological information is also needed.⁶⁵ In an individual patient, an absorbed dose–response relationship, alone, therefore, is not adequately predictive of toxicity. In a larger, but similar patient population, the background of prior treatment, marrow reserve, and the discrepancy between calculation assumptions and true patient parameters are averaged out so that a relationship between dose and toxicity may be more closely correlated. It is important to note that despite these limitations, absorbed dose is still a better predictor of toxicity than administered activity.⁵⁷

X. DISCUSSION

As evinced by the multifaceted issues covered in this work, estimation of red marrow dose, when the administered agent associates with a marrow component, requires consideration of a large number of factors. The difficulties lie both in obtaining the relevant biological information (e.g., kinetics, spatial distribution, geometry) and in estimating energy deposition given the intricate geometry of the marrow. Even if detailed biodistribution data are available and Monte Carlo simulations are used to estimate absorbed dose, the additional variables of marrow reserve and heterogeneity of radiosensitivity remain. In this work, we have examined the various aspects of marrow dosimetry when the agent binds to marrow components. A framework is presented by which various levels of detail regarding the biodistribution of a particular agent may be used to estimate red marrow absorbed dose. This must then be coupled to a method of assessing the effects of prior treatment on marrow radiosensitivity.

Our work concludes with a series of specific recommendations for assessing the potential marrow toxicity of a new therapeutic agent and also for estimating marrow absorbed dose. We have highlighted the distinction between assessing toxicity and performing marrow dosimetry. Toxicity of new agents is assessed with phase I trials, not with dosimetry. Dosimetry is of primary importance in helping establish the initial activity or dose level of a phase I trial. A number of dose escalation variables have been examined for phase I

studies in radioimmunotherapy, including administered activity, activity per surface area, per mass, and also per whole-body or red marrow absorbed dose. If the latter two escalation variables are chosen, then dosimetry is clearly an integral part of the phase I study. Such a study design will, most likely, require a pretherapy trace-labeled administration of the antibody for obtaining patient-specific pharmacokinetics.^{54,64,160} If not selected as a dose escalation variable, red marrow dosimetry becomes essential after a phase I trial has been completed. The pharmacokinetic and toxicity information obtained from such a trial may be used to perform absorbed dose estimates that may then be used to help guide future trials toward more promising approaches or dosage regimens. Toward this objective, we have provided a set of “protocol-specific” recommendations for red marrow dosimetry. In these recommendations we describe clinically implementable procedures that yield the minimum information required for estimating red marrow dose when the administered agent targets a marrow component. In each case, the recommendations reflect an acknowledgment of the logistic and, more recently, financial limitations that are placed on phase I clinical trials. It is important to note that the recommendations that are outlined represent the minimum required *if antibody binds to a cellular component of the marrow, blood, or bone*. The recommendations do not represent the ideal template for performing red marrow dosimetry. In each case, more sophisticated techniques (in attenuation or scatter correction, for example) and the collection of additional data (bone marrow biopsies, additional imaging time points, or SPECT, for example) will provide more accurate estimates of red marrow dose.

As advances continue in our ability to obtain quantitative information, *in vivo*, and as more realistic models are implemented to assess energy deposition in a variety of bone marrow targets from a variety of sources, the utility of red marrow dosimetry will be bounded by our understanding of the radiobiological aspects of marrow response to radiation following prior radio- or chemotherapy. Improvements in this area are needed before a more reliable patient-specific predictive index of marrow toxicity can be established.

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