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Establishing a Clinically Meaningful Predictive Model of Hematologic Toxicity in Nonmyeloablative Targeted Radiotherapy: Practical Aspects and Limitations of Red Marrow Dosimetry

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SUMMATION

In either heavily pretreated or previously untreated patient populations, dosimetry holds the promise of playing an integral role in the physician's ability to adjust therapeutic activity prescriptions to limit excessive hematologic toxicity in individual patients. However, red marrow absorbed doses have not been highly predictive of hematopoietic toxicity. Although the accuracy of red marrow dose estimates is expected to improve as more patient-specific models are implemented, these model-calculated absorbed doses more than likely will have to be adjusted by parameters that adequately characterize bone marrow tolerance in the heavily pretreated patients most likely to receive nonmyeloablative radiolabeled antibody therapy. Models need to be established that consider not only absorbed dose but also parameters that are indicative of pretherapy bone marrow reserve and radiosensitivity so that a clinically meaningful predictive model of hematologic toxicity can be established.

Key words: *dosimetry; bone marrow; radionuclide therapy*

INTRODUCTION

The basic goal of targeted radiotherapy is to ensure that the appropriate activity is administered to the patient to deliver a radiation-absorbed dose to diseased tissues that will produce an effective treatment outcome without causing undesired effects in healthy tissues. The dose-limiting toxicity associated with most of these radiolabeled agents, particularly radioimmunotherapy (RIT), without hematopoietic stem cell support is myelosuppression. As a result, many investigators have evaluated a variety of techniques to develop dose-toxicity relationships. Many believe that the "optimal" approach is based on red marrow dosimetry, and it is recommended that a consistent red marrow dosimetry model be employed in all cases. The results from a host of clinical trials during the past 2 decades suggest that activity-based, as well as total-body dosimetry, methods, have performed as, well as, or better than, red marrow dosimetry, methods in many cases. Thus,

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the most practical and appropriate approach to limit hematologic toxicity may vary, depending on its applicability for a particular radiolabeled antibody treatment in a given patient population, if justified based on comparison with the standard dosimetry model result.

The blood-based and image-based marrow dosimetry approaches will be critiqued and compared to total-body absorbed dose and activity-based methods. The ability of these approaches to predict hematologic toxicity in heavily pretreated and previously untreated patient populations will be compared. While dosimetry methods can be expected to improve significantly, no method based on radiation dose only is likely to account for differing bone marrow reserve and radiosensitivity in the heavily pretreated patient populations likely to receive RIT. Therefore, the need for a reliable method of assessing pretherapy bone marrow reserve coupled with radiation-absorbed dose to establish a clinically meaningful and practical predictive model of hematologic toxicity will be discussed.

Blood-Based Red Marrow Dosimetry

Currently, a widely accepted approach for estimating a red marrow absorbed dose involves a pretherapy tracer administration of the radiotherapeutic agent and a two-component equation[1,2] for those agents that do not bind to any blood, marrow, or bone elements in patients whose disease does not include significant bone marrow or bone involvement. The first component reflects the red marrow self-dose contribution associated with the activity distributed within the extracellular fluid space of the red marrow owing to the circulating blood activity, and the second component reflects the absorbed dose contribution associated with the activity in the remainder of the body, according to:

$$D_{RM} = \tilde{A}_{RM}\, S(RM \leftarrow RM)_{patient} + \tilde{A}_{RB} \times S(RM \leftarrow RB)_{patient} \quad (1)$$

where D_{RM} is the red marrow dose estimate (mGy), $\tilde{A}_{RM}$ is the red marrow cumulated activity (MBq s), $\tilde{A}_{RB}$ is the remainder of the body cumulated activity (MBq s) obtained by subtracting the red marrow value, $\tilde{A}_{RM}$, from the total body value, $\tilde{A}_{TB}$ (MBq s), $S(RM \leftarrow RM)_{patient}$ is the patient-specific red marrow-to-red marrow S-value (mGy/MBq s), and $S(RM \leftarrow RB)_{patient}$ is the patient-specific remainder of the body-to-red marrow S-value (mGy/MBq s). Most investigators have used 1 of 2 dosimetric phantoms, namely Medical Internal Radiation Dose (MIRD) 11[3] or MIRDOSE 3,[4] for the needed S-values and phantom masses in Equation 1. The model need only consider male-only masses and S values.[5] The red marrow mass of the adult male phantom is 1.5 kg and 1.12 kg for MIRD 11 and MIRDOSE 3, respectively, and the total-body mass is 69.88 kg and 73.7 kg for MIRD 11 and MIRDOSE 3, respectively. It would seem more reasonable to use MIRDOSE, or potentially, Organ Level INternal Dose Assessment (OLINDA),[6] S-values and phantom-mass values to accommodate a standard method, as many radionuclides currently in use do not appear in MIRD 11.

The red marrow cumulated activity, $\tilde{A}_{RM}$, in Equation 1 is generally determined by:

$$\tilde{A}_{RM} = [\tilde{A}_{blood}] \times RMBLR \times m_{RM\text{-}patient} \quad (2)$$

where $[\tilde{A}_{blood}]$ is the blood-cumulated activity concentration (MBq s/kg) obtained from serial whole-blood sampling and analysis of the resulting blood activity concentration-time curve and $m_{RM\text{-}patient}$ is the red marrow mass (kg) of the patient The patient-specific red marrow mass is difficult to assess directly, and is typically assumed to vary as a function of patient weight:

$$m_{RM\text{-}patient} = m_{RM\text{-}phantom} \times \left(\frac{m_{TB\text{-}patient}}{m_{TB\text{-}phantom}} \right) \quad (3)$$

The RMBLR is a correction factor representing the marrow-to-blood activity concentration ratio. Originally, the correction factor, RMBLR, was set at unity,[1] but other investigators have shown this value to be too conservative.[7–10] There are currently two basic, practical methods that are most often used to estimate the RMBLR: (1) use of a constant, time-invariant value, such as 0.32;[2,5] and (2) use of a variable, time-invariant value based on RMECFF/(1-hct).[10] The RMECFF, red marrow extracellular fluid fraction, is generally assumed to have a constant value of 0.19, a value obtained from a study of the albumin space in the red marrow of rabbit femur but, importantly, a value not intended for use in patients whose marrow has been compromised by therapy.[10] Because the majority of patients receiving radiolabeled monoclonal antibody therapy (using either commercially available or investigational agents) have undergone prior therapies resulting in vastly differing marrow reserves and radiosensitivities, assigning a value of 0.19 to all patients as the

starting point for the necessary determination of the RM-to-blood activity concentration ratio is of questionable clinical relevance. In a study comparing the use of 0.19/(1-hct) to a fixed value of 0.32, equivalent dose-toxicity correlations were observed.[5] For these reasons, the use of a constant RMBLR of 0.32 is used in this paper.

As indicated by Equations 1 and 2, the red marrow absorbed radiation dose is estimated in patients based on the measured cumulated activity concentration in the whole blood and the measured cumulated activity in the total body. The relative contribution of each of these two components to the red marrow dose estimate is dependent upon the total body-to-blood cumulated activity ratio.[11] Additional distinguishable source-organ contributions could also be included;[2] however, their expected contribution to a red marrow dose has been estimated to be on the order of 5%, as long as the radiotherapeutic agent is not concentrated in any one or two particular organs. Thus, the use of the remainder of the body approach to represent all photon contributions to red marrow dose from distinguishable source organs is appropriate. However, if some tissues have exceptionally large uptake and prolonged retention, it may be necessary to explicitly include these source organs in the determination of red marrow dose.[12] In these cases, Equation 1 would need to be modified accordingly.

The patient-specific red marrow and remainder of the body S-values in Equation 1 are determined as:

$$S(RM \leftarrow RM)_{patient} = S(RM \leftarrow RM)_{phantom} \times \left(\frac{m_{RM\text{-}phantom}}{m_{RM\text{-}patient}} \right) \quad (4)$$

$$S(RM \leftarrow RB)_{patient} = \left\{ S(RM \leftarrow TB)_{phantom} \times \left(\frac{m_{TB}}{m_{TB} - m_{RM}} \right) - S(RM \leftarrow RM)_{phantom} \times \left(\frac{m_{RM}}{m_{TB} - m_{RM}} \right) \right\} \times \left(\frac{m_{RM\text{-}phantom}}{m_{RM\text{-}patient}} \right) \quad (5)$$

It should be noted that the remainder of the body S-value (and thus, the remainder of the body term in Equation 1) is patient mass–dependent, as it contains the multiplicative factor of $m_{RM\text{-}phantom}/m_{RM\text{-}patient}$, which, based on Equation 3, can be approximated as $m_{TB\text{-}phantom}/m_{TB\text{-}patient}$, to correct for patient-mass variations from assumed phantom values. This same multiplicative factor results in a marrow self-dose term in Equation 1 that is patient mass–independent. The RM and TB masses, m_{RM} and m_{TB}, not specified in Equation 5 as to whether they are actual patient masses or phantom masses, is the result of the fact that the use of either set of values will generate the same result (this is because the estimated patient RM mass is obtained through adjustment of the phantom RM mass based on patient TB mass, as indicated by Equation 3). It can easily be demonstrated that:

$$\left(\frac{m_{TB\text{-}patient}}{m_{TB\text{-}patient} - m_{RM\text{-}patient}} \right) = \left(\frac{m_{TB\text{-}phantom}}{m_{TB\text{-}phantom} - m_{RM\text{-}phantom}} \right) \text{ and}$$

$$\left(\frac{m_{RM\text{-}patient}}{m_{TB\text{-}patient} - m_{RM\text{-}patient}} \right) = \left(\frac{m_{RM\text{-}phantom}}{m_{TB\text{-}phantom} - m_{RM\text{-}phantom}} \right) \quad (6)$$

Combining Equations 1–5, and using MIRDOSE 3 masses and a constant RMBLR of 0.32, results in the following expression for red marrow dose, D_{RM} (mGy):

$$\begin{aligned} D_{RM} &= [\tilde{A}_{blood}] \times 0.32 \times 1.12 \times \left(\frac{m_{TB\text{-}patient}}{73.7} \right) \times S(RM \leftarrow RM)_{phantom} \times \left(\frac{73.7}{m_{TB\text{-}patient}} \right) \\ &+ \left[\tilde{A}_{TB} - [\tilde{A}_{blood}] \times 0.32 \times 1.12 \times \left(\frac{m_{TB\text{-}patient}}{73.7} \right) \right] \\ &\times \left\{ S(RM \leftarrow TB)_{phantom} \times \frac{73.7}{73.7 - 1.12} - S(RM \leftarrow RM)_{phantom} \times \frac{1.12}{73.7 - 1.12} \right\} \times \frac{73.7}{m_{TB\text{-}patient}} \\ &= [\tilde{A}_{blood}] \times 0.32 \times 1.12 \times S\ (RM \leftarrow RM)_{phantom} \\ &+ [\tilde{A}_{TB}/m_{TB\text{-}patient} - [\tilde{A}_{blood}] \times 0.32 \times 1.12/73.7] \\ &\times \left\{ S(RM \leftarrow TB)_{phantom} \times \left(\frac{73.7}{73.7 - 1.12} \right) \right. \end{aligned}$$

$$- S(RM \leftarrow RM)_{phantom} \times \left(\frac{1.12}{73.7 - 1.12} \right) \Bigg\} \times 73.7 \quad (7)$$

Equation 7 represents a practical implementation for the determination of red marrow absorbed dose estimates when use of the two-component blood-based model is appropriate. For pure beta-emitting radionuclides, such as ^{90}Y, ^{89}Sr, and ^{32}P, the remainder of the body term is negligible (the remainder of the body S-value can be set to zero) and only consideration of the marrow self-dose term is necessary. For those radionuclides with a significant penetrating photon component, such as ^{131}I and ^{186}Re, the contribution of the remainder of the body term must be taken into account.

Finally, red marrow absorbed dose can be estimated using Equation 7 and MIRDOSE 3 S-values (mGy/MBq s) for ^{131}I, ^{186}Re, and ^{90}Y, three commonly used beta-emitting radionuclides:

$$^{131}I: \quad D_{RM} = 5.15E\text{-}06 \{[\tilde{A}_{blood}] + [\tilde{A}_{TB}] \times 7.5\} \quad (8)$$

$$^{186}Re: \quad D_{RM} = 8.13E\text{-}06 \{[\tilde{A}_{blood}] + [\tilde{A}_{TB}] \times 3.8\} \quad (9)$$

$$^{90}Y: \quad D_{RM} = 2.10E\text{-}05 [\tilde{A}_{blood}] \quad (10)$$

where $[\tilde{A}_{TB}]$ is equal to $\tilde{A}_{TB}/m_{TB\text{-}patient}$ and is the cumulated activity concentration in the total body (MBq s/kg).

Equations 8–10 illustrate the simplicity of the two-component blood-based method for red marrow dose estimation. This dose-based approach takes into account individual patient biokinetics and theoretically, at least, should provide a more rational basis for targeted radiotherapy treatment prescriptions when hematological toxicity is dose-limiting. The typical treatment-planning paradigm involves the determination of the treatment activity prescription (MBq) by dividing the prescribed red marrow radiation dose (mGy) by the anticipated radiation dose, as estimated by the pretherapy tracer study. Once a maximum tolerated dose in terms of absorbed dose is established, it potentially can be universally applied to all antibody constructs (e.g., humanized, chimeric, whole IgG, fragments) and all beta-emitting radionuclides. This would not be true for administered activity-based tolerance limits, as the toxicity predictors of administered activity or administered activity adjusted for body weight or body surface area would likely have to be redefined for each radionuclide-antibody entity because of a variation in clearance kinetics (e.g., an activity-based treatment prescription for a radiolabeled antibody with prolonged uptake and retention, such as a humanized construct, would likely be lower than for a radiolabeled antibody with a faster rate of clearance, such as an antibody fragment).[13]

Image-Based Red Marrow Dosimetry

When there is specific binding of antibodies to cellular components of the marrow, blood, or bone, radiolabeled antibody blood pharmacokinetics cannot be related to the marrow, and the use of Equations 2 and 7–10 are not valid. When marrow targeting occurs, serial marrow imaging is obtained after a pretherapy tracer administration of the therapeutic agent and quantitative analyses, typically involving lumbar spine or sacral regions of interest (ROIs), are performed to estimate the associated absorbed-dose component.[7,14–16] Patients with better marrow visualization generally have greater red marrow doses than those with poorer visualization.[14] Imaging methods will produce similar results to those obtained using the blood-based method if marrow targeting is low.[8] However, depending on the uptake and/or clearance half-times, specific marrow targeting can result in substantial increases to red marrow absorbed dose relative to that from the blood and body.[11,14,17,18] The prediction of myelotoxicity has been shown to be substantially improved using the image-based estimate of the red marrow absorbed dose (dose-toxicity correlation coefficient, r, increased from 0.38 to 0.61).[19]

Image-based dose estimates are subject to large variability owing to their inherent uncertainties, use of a single region assumed to be representative of the entire marrow, and can be misleading because they represent macroscopic, global values that do not reflect the heterogeneity of the marrow itself or the radionuclide distribution. Nonuniform radiation-dose distributions may be responsible for the diversity observed in radiobiologic responses.[15,20,21] Regional marrow dose obtained by the analysis of different marrow regions in the same patient (humerus, femur, lumbar vertebrae) have been shown to differ significantly.[22] Further, bone marrow contains a variety of cells of vastly differing radiosensitivi-

ties. Stem cells, for example, are crucial to hematologic toxicity and may receive a range of radiation-absorbed doses resulting from the cross-dose from targeted marrow cells.[2] (Because of the diffuse nature of micrometastatic deposits in lymphoma and their generally small average diameters compared to the path length of ^{131}I, the dose distribution may be partially "evened out.") Quantitative single photon emission computer tomography (SPECT) or positron emission tomography (PET) may be able to provide the spatial distribution of activity within marrow regions at the voxel level,[23] while detailed analyses of biopsy specimens would be required to assess nonuniformities at the multicellular or cellular levels. Although microdosimetric and voxel-based calculations may be important in certain circumstances, detailed information regarding the location of marrow cells, radionuclide uptake distribution, and its geometrical arrangement may not be available. Because of the considerable time and expertise required to perform image-based red marrow dosimetry, some have employed semiquantitative image interpretation with relatively good success ($r = 0.76$).[24]

Further, adequate evaluation of the effects of the radiation-absorbed dose on the hematopoietic system may require knowledge of the patient's active red marrow mass in the selected regional marrow sites. But the site-specific phantom S-values for a variety of marrow-rich regions are based on single-valued, phantom-specific masses in these regions; no uncertainty is offered with respect to these masses.[4,25] The model S-values were developed to represent an average population, but patients undergoing RIT for which these S-values may be applied have low marrow reserves and techniques are needed to calculate patient-specific S-values. Patient-specific marrow masses are generally not measured; these masses are estimated using adjustments of the phantom masses based on body weight, even though body weight may not correlate with actual marrow masses.[26,27] Based on measurements in individual bones of 11 cadavers, Woodard[27] reported not only mean active marrow masses but also their standard deviation in a number of sites, indicating that the use of a fixed mean value in all cases may result in an uncertainty as large as 60% (based on mean values $\pm$ 2 standard deviations). This is perhaps why marrow mass must be measured and not estimated based on body weight. One study indicated that image-based marrow dose estimates using measured marrow masses were a better predictor of myelotoxicity than conventional image-based estimates ($r = 0.85$ and 0.67, respectively) in a patient population without a significant impact of marrow involvement and previous myelosuppressive chemotherapies (it was noted that this method may not be applicable to pretreated patient populations with marrow involvement).[26] Although these patients received nonmarrow targeting ^{90}Y-antibody therapy, bone marrow was visualized on imaging presumably resulting from activity recycled into the marrow/trabecular bone space after antibody metabolism. This situation is unlike ^{90}Y therapy in non-Hodgkin's lymphoma patients, where marrow targeting is anticipated owing to involvement with disease. There is another reason why bone marrow may be visualized on nuclear medicine images. Most of the antibodies used for the treatment of hematologic malignancies target normal cells that reside in the bone marrow in addition to bone marrow leukemia and lymphoma. Patients who are recovering from chemotherapy may have hyperproliferating bone marrow with enhanced radioantibody uptake evident on imaging studies resulting from binding to an increased number of normal cells and their precursors.[28]

In spite of the above, imaged-based red marrow absorbed dose estimates have proven to be of value and represent a clinically implementable, practical approach. It has been suggested that the average absorbed dose over the whole marrow, and not the regional dose, is the quantity of importance, as it is a more conservative assessment of overall marrow toxicity;[22] this is the basis of the recommended approach that follows. This is because the experience with external beam irradiation suggests that specific sites may be depleted of red marrow without associated morbidity. The hematopoietic bone marrow system, which is spread throughout some 206 skeletal bones, acts and reacts as one organ system.[29] Continuous migration of stem cells through the blood to assure a sufficient stem cell pool size in each bone marrow "subunit" is one of the regulatory mechanisms leading to that observation. Thus, because the stem cell migration dynamics, any dose nonuniformity in a regional marrow site may result in an increased chance of spontaneous recovery of that part of the system.

The average whole-marrow dose can be obtained by: (1) averaging cumulated activity concentration or absorbed dose over multiple regional sites; or (2) using a single site if qualitative

inspection of the pattern of marrow uptake in the images suggests a reasonably homogeneous distribution at this macroscopic level. The same single region may not be able to be used exclusively (e.g., because of overlying disease or if its activity uptake is appreciably elevated). Both methods require that the term for $\tilde{A}_{RM}$ in the conventional blood-based model (Equation 2) be redefined as:

$$\tilde{A}_{RM} = \sum_{i=1}^{n} [\tilde{A}_{RM}]_i / n \times m_{RM\text{-patient}} \quad (2R)$$

where $[\tilde{A}_{RM}]_i$ is the cumulated activity concentration (MBq s/kg) in the ith red marrow regional site and *n* is the number of regional marrow sites (if using a single site, $i = 1$). (If bone uptake is involved, then the marrow absorbed dose estimate should consider two additional source terms: *cortical* and *trabecular bone*.) Equation 2R specifies a mean value; perhaps it should be a weighted mean, if the multiple sites have vastly differing marrow masses). $[\tilde{A}_{RM}]_i$ is equal to $1.443 \times f_i \times A_0 \times T_{e,i}$ where f_i is the fraction of the administered activity, A_0, per unit mass (kg) in the ith regional site ending up as targeted activity uptake and $T_{e,i}$ is the effective half-time (s) in the ith marrow region of interest. The required activity concentrations (i.e., $f \times A_0$) can be obtained by analysis of serial planar images to estimate activity followed by division by phantom-specific regional marrow mass or measured regional marrow mass, or directly from a single SPECT study employing a volume region of interest analysis. Using planar imaging and site-specific phantom masses or SPECT activity concentrations may not accurately reflect the patient's actual red marrow activity concentration. This can only be done with a regional marrow mass determination, perhaps by a separate marrow scintigraphic study or magnetic resonance imaging (MRI)/spectroscopy, but such a determination is not yet clinically justified.[15]

If sufficient analyses are performed for a specific agent in a defined patient population that confirm the finding that regional marrow clearance half-times are similar and approximately equal to total body,[22] $[\tilde{A}_{RM}]$ may be estimated by the average f-value times $\tilde{A}_{TB}$. Substituting this into Equation 2R (and using Equations 1 and 3–5), for ^{131}I, for example, results in a revised Equation 8:

$$D_{RM} = 1.61\text{E-}05 \times f \times \tilde{A}_{TB} + 3.84\text{E-}05 \times [\tilde{A}_{TB}] \quad (8R)$$

Another potentially interesting approach would be to multiply the fractional bone marrow involvement with disease, as determined from a biopsy specimen by $f \times A_0$ (if it were demonstrated that the average "f" varied as a function of bone marrow involvement) and the patient's red marrow mass to obtain the average activity uptake in the entire bone marrow.

Total-Body Dosimetry

Some investigators have shown that the total-body radiation dose is a useful surrogate for the blood-based red marrow dose.[30,31] This is despite the implication that biological response is related to the total energy absorbed in the body; a picture of radiation response that is certainly an oversimplification as the bone marrow is known to be more sensitive to radiation than other organs.[32] The total-body absorbed dose, D_{TB} (mGy), is calculated using the MIRDOSE 3 total body mass as:

$$D_{TB} = \tilde{A}_{TB} \times S\ (TB \leftarrow TB)_{phantom} \times \left(\frac{73.7}{m_{TB\text{-}patient}} \right) = \frac{\tilde{A}_{TB}}{m_{TB\text{-patient}}} [S\ (TB \leftarrow TB)_{phantom} \times 73.7] \quad (11)$$

The total body dose can be estimated using Equation 11 and MIRDOSE 3 S-values for ^{131}I, ^{186}Re, and ^{90}Y:

$$^{131}\text{I:} \quad D_{TB} = 5.21\text{E-}05 \times \frac{\tilde{A}_{TB}}{m_{TB\text{-patient}}} \quad (12)$$

$$^{186}\text{Re:} \quad D_{TB} = 5.64\text{E-}05 \times \frac{\tilde{A}_{TB}}{m_{TB\text{-patient}}} \quad (13)$$

$$^{90}\text{Y:} \quad D_{TB} = 1.50\text{E-}04 \times \frac{\tilde{A}_{TB}}{m_{TB\text{-patient}}} \quad (14)$$

The factor of $\frac{\tilde{A}_{TB}}{m_{TB\text{-patient}}}$ is simply multiplied by a constant term for each radionuclide, independent of the biokinetic differences between total body and blood.

Red Marrow Versus Total-Body Dosimetry

The following analyses assume that use of the blood-based method is appropriate (i.e., there is no specific binding of the administered agent to cellular components of the marrow, blood, or bone). For illustrative purposes and to facilitate comparisons, the red marrow dose (Eq. 7) can be

redefined so that it is in a visually compatible form as the total-body dose (Eq. 11). To accomplish this, two adjustments are necessary. First, the blood cumulated activity concentration, $[\tilde{A}_{blood}]$, is replaced by $\tilde{A}_{blood}/m_{blood\text{-}patient}$, where

$$m_{blood\text{-}patient} = m_{blood\text{-}Reference\ Man} \times \left(\frac{m_{TB\text{-}patient}}{m_{TB\text{-}phantom}}\right) \quad (15)$$

The Reference Man blood mass is 5.5 kg. Second, the blood cumulated activity, $\tilde{A}_{blood}$, is expressed in terms of the total body cumulated activity, $\tilde{A}_{TB}$. That is, since $\tilde{A}_{blood}$ and $\tilde{A}_{TB}$ are independently determined, $\tilde{A}_{TB}/\tilde{A}_{blood}$ can be set equal to x, where x is the measured ratio, and $\tilde{A}_{blood}$ is replaced by $\tilde{A}_{TB}/x$. With these two modifications, Equation 7 becomes:

$$\begin{aligned} D_{RM} &= (\tilde{A}_{TB}/x) \times 0.32 \times 1.12 \times 73.7/(5.5 \times m_{TB\text{-}patient}) \times S\ (RM{\leftarrow}RM)_{phantom} \\ &+ [\tilde{A}_{TB}/m_{TB\text{-}patient} - (\tilde{A}_{TB}/x) \times 0.32 \times 1.12/(5.5 \times m_{TB\text{-}patient})] \\ &\times \left\{S(RM{\leftarrow}TB)_{phantom} \times \left(\frac{73.7}{73.7 - 1.12)} - S(RM{\leftarrow}RM\right)_{phantom} \times \left(\frac{1.12}{73.7 - 1.12}\right)\right\} \times 73.7 \\ &= \frac{\tilde{A}_{TB}}{m_{TB\text{-}patient}} \left[\left(\frac{4.80}{x}\right) \times S\ (RM{\leftarrow}RM)_{phantom} + \left[1 - \frac{0.0652}{x}\right] \right. \\ &\left. \times \{S(RM{\leftarrow}TB)_{phantom} \times 74.84 - S(RM{\leftarrow}RM)_{phantom} \times 1.137\}\right] \quad (16) \end{aligned}$$

Equation 16 can be used to estimate bone marrow doses for ^{131}I, ^{186}Re, and ^{90}Y. Upon substitution of MIRDOSE 3 S-values:

$$^{131}\text{I: } D_{RM} = \frac{\tilde{A}_{TB}}{m_{TB\text{-}patient}} \left\{\left(\frac{7.16E-05}{x}\right) + \left[1 - \left(\frac{0.0652}{x}\right)\right] \times 3.84\text{E-}05\right\} \quad (17)$$

$$^{186}\text{Re: } D_{RM} = \frac{\tilde{A}_{TB}}{m_{TB\text{-}patient}} \left\{\left(\frac{1.11E-04}{x}\right) + \left[1 - \left(\frac{0.0652}{x}\right)\right] \times 3.09\text{E-}05\right\} \quad (18)$$

$$^{90}\text{Y: } D_{RM} = \frac{\tilde{A}_{TB}}{m_{TB\text{-}patient}} \left\{\left(\frac{2.82E-04}{x}\right)\right\} \quad (19)$$

Thus, the red marrow dose is simply the factor of $\frac{\tilde{A}_{TB}}{m_{TB\text{-}patient}}$ multiplied by a term dependent upon the measured total body-to-blood cumulated activity ratio, x, for each radionuclide. For ^{131}I, ^{186}Re, and ^{90}Y, as shown in Table 1 for values of x ranging from 1 to 10, the x-dependent term in Equations 17–19 decreases, as expected, as a function of x. Therefore, the red marrow absorbed dose will decrease in a similar fashion, as multiplication of the tabulated x-terms by $\frac{\tilde{A}_{TB}}{m_{TB\text{-}patient}}$ will result in the red marrow dose. Also, as shown in Table 1, the contribution of the remainder of the body component to the total red marrow dose (indicated by %RB) increases as a

Table 1. Dependence of Red Marrow Dose on Total Body-to-Blood Cumulated Activity Ratio

	$\tilde{A}_{TB}/\tilde{A}_{blood}$ ratio									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
^{131}I	1.07	0.73	0.61	0.56	0.52	0.50	0.48	0.47	0.46	0.45
%RB	33.4	50.9	61.1	67.8	72.6	76.1	78.8	81.0	82.7	84.2
^{186}Re	1.40	0.85	0.67	0.58	0.53	0.49	0.46	0.45	0.43	0.42
%RB	20.6	35.0	45.0	52.3	57.9	62.3	65.9	68.8	71.3	73.4
^{90}Y	2.82	1.41	0.94	0.70	0.56	0.47	0.40	0.35	0.31	0.28

The first row for each radionuclide represents the value of the x-dependent term in Equations 17–19; each value is $\times 10^{-4}$. The second row for ^{131}I and ^{186}Re represents the percent remainder of the body contribution to the total red marrow dose (%RB); this contribution is 0% for ^{90}Y.

function of x (conversely, the red marrow self-dose contribution becomes progressively less significant). At higher ratios, total-body dose may be a useful surrogate for red marrow dose for ^{131}I agents, as the marrow dose contribution from the blood is small compared to the marrow-radiation dose contributed by the body. Furthermore, there is usually a moderate correlation between the total-body and red marrow dose for these agents (i.e., total body biokinetics are correlated with blood pharmacokinetics).[33] The use of total body dose may not be appropriate for ^{186}Re radiolabeled agents. For ^{90}Y-labeled monoclonal antibodies, poor correlation is expected between the total-body and red marrow dose because most of the radioactivity is retained in the body independent of the blood pharmacokinetics.[17,33] Of course, this type of analysis would have to be performed for all other radionuclide agents before making any claim that a total-body dose approach might be applied successfully.

The ratios of red marrow-to-total body dose as calculated using Equations 17-19 and 12–14 (i.e., Equation 17 divided by Equation 12, Equation 18 divided by Equation 13, and Equation 19 divided by Equation 14) for ^{131}I,^{186}Re, and ^{90}Y, respectively, as a function of total body-to-blood cumulated activity ratio, x, are given in Table 2.

The values in Table 2 indicate that at total body-to-blood ratios of 4 and higher, the total-body dose may indeed be a useful surrogate for red marrow dose for ^{131}I, as the 2 calculated dose values are within approximately 10% of each other. In addition, if the range of total body-to-blood ratio is documented as being sufficiently narrow across patients, regardless of x, or if total-body clearance is highly correlated with blood clearance, then a good argument could also be advanced to eliminate the need for blood sampling. The two-component red marrow dose approach could be used, but blood measurements would not be necessary, as $\tilde{A}_{blood}$ could be replaced with the value of $\tilde{A}_{TB}/x$. One study has already demonstrated the utility of using blood pharmacokinetic estimates from total-body count data in a series of patients where the range of individual total body-to-blood ratios was sufficiently narrow, such that the assumption of a single value for all patients provided results within acceptable uncertainty limits.[34]

In a study of ^{131}I antibody therapy in a subset of metastatic renal cell carcinoma patients with minimal prior therapy, a novel "moving window" approach was used to examine the probability of experiencing toxicity within a range of values for various toxicity predictor variables.[13] Well-defined relationships between hematologic toxicity were observed not only for the red marrow dose but also for the total-body dose. This study also suggested that the use of an activity-based specification of treatment might also be reasonable. On the other hand, the use of ^{131}I-CC49 in a prostate cancer patient cohort without any prior myelosuppressive chemotherapy demonstrated that the marrow dose correlated with the platelet nadir ($r = 0.74$) significantly better than did the total-body dose.[35] In this case, the correlation of total body and blood clearance was poor and the marrow self-dose component predominated the dose calculation.

Because ^{186}Re has a significantly higher nonpenetrating component than ^{131}I and ^{90}Y has an essentially 100% nonpenetrating component, it is less likely that the total-body dose will be a reliable indicator of marrow toxicity for these two radionuclides, as indicated by the values in Table 2. However, total-body dose may be a useful surrogate measure for ^{186}Re if "x" ratios are in the range of 4–6. This has been demonstrated for ^{90}Y-DOTA-biotin with pretargeted NR-LU-10/streptavidin, an approach that removes radioactivity from the blood more rapidly than does conventional radioimmunotherapy.[36] The standard blood-based red marrow dose correlated better with marrow toxicity than the total-body radiation dose; the correlation increased when all

Table 2. Dependence of Red Marrow-to-Total Body Absorbed Dose Ratio on Total Body-to-Blood Cumulated Activity Ratio

	$\tilde{A}_{TB}/\tilde{A}_{blood}$ *ratio*									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
^{131}I	2.06	1.40	1.18	1.07	1.00	0.96	0.93	0.90	0.88	0.87
^{186}Re	2.48	1.51	1.19	1.03	0.93	0.87	0.82	0.79	0.76	0.74
^{90}Y	1.88	0.94	0.63	0.47	0.38	0.31	0.27	0.24	0.21	0.19

heavily pretreated patients were excluded from the analysis. In another study involving ^{186}Re-labeled monoclonal antibody, essentially equivalent dose-toxicity correlations were observed for the red marrow dose, total-body dose, and administered activity adjusted for weight or body surface area, regardless whether the patient population was pretreated or untreated (except for the total-body dose, where the r value increased from 0.72 to 0.87 in previously untreated patients).[37]

The analyses and studies referred to above indicate that the most practical and appropriate approach to limit hematologic toxicity may vary depending on its applicability for a particular radiolabeled antibody treatment in a given patient population, if justified based on comparison with a consistent red marrow dosimetry model result.

Maximum Tolerated Dose and Anticipated Dose-Toxicity Correlations

The maximum tolerated dose (MTD) for a particular targeted radiotherapy agent in a nonmyeloablative setting when hematologic toxicity is dose limiting is determined during a phase I clinical trial. The most commonly used definition of the MTD is the dose level at which dose-limiting hematologic toxicity does not occur in more than 1 of 6 patients. The dose-limiting toxicity (DLT) defined for many nonmyeloablative protocols typically allows for grade 3 and even grade 4 hematologic toxicity of limited duration if self-resolving. Thus, at the MTD, 1 of 6 patients would be expected to exceed this DLT limit and likely require an intervention, while it is expected that most patients will be just below this limit and experience transient and manageable marrow suppression. Typically, administered activity (or activity per patient weight or body-surface area), and not dosimetry, is selected as the dose escalation variable, but according to FDA requirements, all phase I studies using a radioactive procedure must include studies which will obtain sufficient data for dosimetry calculations. Regardless of the dose-escalation method used (activity, macroscopic radiation dose, cellular radiation dose), the DLT will always be a clinical endpoint.

While the hope is that the administered activity at the MTD would be the highest allowed in every patient, there may be a sizable portion of patients who have considerably less toxicity (e.g., $\leq$grade 2) than allowed at the treatment MTD. The MTD defined in the initial phase I testing may undergo additional adjustments during phase II, but most often these adjustments are made to ensure that the population exceeding the DLT is minimized rather than trying to make adjustments that would optimize the number of patients being treated at the maximum toxicity allowed. This is the challenge for the dosimetric approaches provided in this work (i.e., can they provide a more reliable approach to optimize the number of patients treated at the maximum toxicity level and minimize the number of patients experiencing more severe hematologic toxicity?). It would be prudent to first examine existing data to assess whether those patients experiencing a less than or equal to grade 2 toxicity are, in fact, less responsive to treatment. If so, are these patients likely to benefit more if they were given a somewhat higher treatment prescription to result in a grade 3 to 4 hematologic toxicity? Existing dosimetry data (either retrospective or prospective) may be able to identify a potentially more predictive dosing model that would then require evaluation in a phase I to II safety-efficacy clinical trial.

Spatial Level Scale for Dosimetry

Internal dosimetry calculations can be performed over a broad range of target dimensions: whole organs, suborgan regions, small-scale tissue (voxel) regions, multicellular clusters, single cells, and even subcellular regions.[23] Nonuniformities in activity deposition and their effect on the resultant absorbed-dose distributions may occur at all these levels. At a macroscopic level, the radiolabeled agents may appear to be uniformly distributed throughout the tissue, but on closer inspection, not all cells in the tissue may be labeled. One study examined this issue using a cell-culture model to assess the impact of nonuniformities at the multicellular level on the lethal effects of ^{131}I.[38] The results indicated that the mean absorbed dose to a tissue element may not be a suitable quantity for use in predicting the biologic effects of incorporated ^{131}I if the activity distribution is nonuniform at the multicellular level; rather, cellular and multicellular dosimetry approaches may be necessary. This observation certainly impacts the image-based red marrow approaches, as discussed previously.

When use of the blood-based dosimetry method is appropriate, there is no cell labeling and the macroscopically estimated marrow dose through use of Equation 7 is expected to work

reasonably well. In fact, a macroscopically determined bone marrow radiation absorbed dose has proven to be useful in limiting severe hematologic toxicity in thyroid cancer patients treated with $Na^{131}I$. Although radioiodine therapy for thyroid malignancy routinely relies on clinical parameters other than individualized dosimetry to ensure safety, a recent study employed a dosimetry-guided radioactive iodine treatment in patients with metastatic differentiated thyroid cancer. This study, where the administered ^{131}I therapeutic activity, as high as 38.5 GBq, was based on delivering a 3-Gy bone marrow absorbed dose using the blood-based dosimetry method, demonstrated that all patients developed transient bone marrow depression but no patient experienced permanent bone marrow failure.[39] This putative "safe" 3-Gy dose limit was established in an essentially previously untreated patient population and might be applicable to untreated patient populations receiving other forms of targeted radionuclide therapy. It must be pointed out that unlike the treatment of thyroid cancer with radioiodine, which exhibits a very wide therapeutic "window" (i.e., the difference between the radiation dose delivered to the tumor and the radiosensitive bone marrow), RIT typically exhibits a much lower therapeutic "window" and, therefore, optimization of the therapeutic administration becomes more critical.[40]

Treatment Prescription

Marrow dosimetry should be the cornerstone upon which to build comprehensive, yet simple, algorithms for managing targeted radiotherapy patients. This is because the critical dose-limiting organ is the bone marrow. Nevertheless, the calculated red marrow absorbed dose has not been highly predictive of the hematologic toxicity observed in many patient populations studied.[5,41,42] Patients receiving the same model-calculated red marrow dose often experience different grades of toxicity, with myelosuppression being most pronounced in patients with compromised bone marrow resulting from prior chemotherapy. Some investigators, as previously discussed, have shown that the use of the total-body dose as a surrogate for the red marrow dose[30,31] or administered activity adjusted for patient body weight[43] or surface area[44] have been useful for limiting hematologic toxicity, while others have clearly demonstrated a lack of predictive value for marrow toxicity from adjusted administered activity levels or total-body absorbed doses.[45] As a result, unlike external beam radiation therapy, where patient-specific treatment planning is performed in order to ensure delivery of the tumor radiation dose prescribed to optimize the probability of tumor control relative to normal tissue complications, there is no standard approach for the treatment prescription of RIT. Treatment may be prescribed in terms of administered activity, administered activity adjusted for patient specific parameters (e.g., body weight or surface area), or the absorbed radiation dose. If a model, appropriately validated, could accurately predict those patients likely to experience a less than or equal to grade 2 hematologic toxicity (assuming, importantly, that these patients are likely to exhibit reduced treatment efficacy) and those patients likely to exceed the DLT limit, it may be of important clinical benefit.

Activity-based methods (administered activity or activity adjusted for patient body weight or surface area) are the simplest approaches to treatment prescription for RIT and are, typically, the starting point for establishing a meaningful predictive model for hematologic toxicity. For those therapeutic agents that do not bind to cellular components of the marrow, blood, or bone, the next levels involving dosimetric complexity are the estimation of the total-body dose using Equation 11 and the blood-based, whole-marrow average radiation dose as estimated using Equation 7. For those agents that bind to any of the cellular components previously mentioned—and, therefore, specific marrow targeting is an issue—the next level of dosimetric complexity is image-based regional average marrow dose estimates, as determined employing either a single representative regional marrow site or multiple regional sites using Equations 1, 2R, and 3–5. There is certainly room for improvement in the accuracy of macroscopic imaged-based methods and a potential need for more cellular approaches, but, for now, the former methods—"calibrated" by observed clinical outcomes—represent the most reasonable approach. The variability in the marrow-targeted dose component can be minimized if only patients with a limited bone marrow involvement with disease are allowed to be treated.

The balance between accuracy and clinical feasibility is yet to be established, but is necessary for the purpose of establishing practical and clinically meaningful approaches to predicting hematologic toxicity in a nonmyeloablative setting. Absorbed dose methods require a pretherapy ad-

ministration to establish patient-specific biokinetic parameters, while activity-based methods are simple and require no individualized dosimetry. Ultimately, the selected approach to treatment prescription should be accurate and produce meaningful clinical results. It should not be based on the simplest and/or the most clinically feasible approach. The use of more, or of less, complex models should be based on comparisons with the results obtained using a consistent red marrow dosimetry approach. It there are minimal variations in interpatient biokinetics for a particular targeted radiotherapy in a defined patient population, it may be reasonable to use an activity-based approach as a basis for treatment prescription.[13] In those cases where there are significant interpatient biodistribution differences and there is no bone marrow visualization, it is likely that there is no active accumulation of radioactivity in the marrow elements and the blood-based red marrow or total-body dose approaches may be reasonable. Nuclear medicine imaging is very important and valuable in this regard. Bone marrow visualization implies that the blood-based marrow absorbed dose estimate may be on the low side and considerations of the increased dose component resulting from targeted marrow uptake should be addressed using image-based approaches.

The Need to Merge Physics with Biology

Although MIRD-type dose estimates are time-honored and tested in the crucible of clinical experience, the absorbed dose is only a surrogate for the issue of clinical importance, the biological response of the patient. There is an important need to develop and use biophysical models in an attempt to translate absorbed dose information into estimates of biological impact. Clinical evidence suggests that it is the heterogeneity of patients likely to receive targeted radiotherapy, particularly with respect to prior cytotoxic chemotherapy, and not the intractability or impracticality of marrow radiation dosimetry, that undermines the derivation of meaningful (i.e., predictive) dose-response relationships for myelotoxicity.[46]

One reason for the limited dose-toxicity correlations observed may be the accuracy of the red marrow absorbed dose estimates obtained using the blood-based and image-based models. It may be necessary to more directly determine the cumulated activity in the red marrow, as the current methodology (i.e., use of Equation 2) may not adequately address the variability and time-dependence[47] of the RMBLR. To better characterize marrow biokinetics, scintillation camera image-based analyses[7,9] or compartmental modeling techniques[48] could be used. Alternatively, magnetic resonance spectroscopy may be able to provide a more patient-specific estimate of the RMECFF for use in estimating the RMBLR factor.[49] These approaches would certainly result in more patient-specific, and thus, more accurate dose estimates. However, one study has suggested that, because of the wide patient-to-patient variation in response to low-dose-rate radiation, it might be difficult to predict toxicity even if absorbed dose estimates are shown to be accurate,[37] an observation that leads to a second reason. Hematologic toxicity may result from factors not entirely explained by pharmacokinetics and dosimetric variables alone.

Individuals' biologic response to radiation may vary because of inherent interpatient differences, decreased bone marrow reserve, and increased radiosensitivity resulting from prior cytotoxic therapies. Thus, regardless of accuracy, no marrow dosimetry method (or total-body dose or activity-based approach) presented in the previous sections accounts for these biologic parameters. Because a decrease in marrow reserve, a known important factor in the bone marrow's ability to withstand cytotoxic chemotherapy, is associated with a decrease in stem cells' repopulating ability,[50] it is highly likely that the same radiation dose in a patient with decreased, compared to normal, reserve will have a greater effect. Thus, the treatment prescription in these patients would most likely have to be modified to deliver a lower marrow radiation absorbed dose.

Establishing a Clinically Relevant Practical Method to Limit Hematologic Toxicity

Managing hematologic toxicity is an everyday event for medical oncologists, but despite this, there are no good models for predicting toxicity.[50] For the most part, experience in administering multidose regimens provides the ability to adjust or delay doses. Predictive toxicity models are much more important for RIT treatment, as it is typically given as a single intervention. The identification and measurement of meaningful risk factors (i.e., marrow reserve/radiosensitivity), as part of a predictive toxicity model to enable a pretherapy assessment of the likelihood and degree of hematologic toxicity would be of important clini-

cal benefit. A reliable method of assessing pretherapy bone marrow reserve coupled with absorbed dose has been suggested to be the optimal approach to treatment prescription for RIT in cases where hematologic toxicity is dose-limiting.[13] On a practical level, there is no advantage to using fancy models and mathematics if simpler equations and methods are able to provide a meaningful predictive model of hematologic toxicity and offer a reasonable approach to incorporate known objective measures of bone-marrow toxicity into treatment-plan optimization and the design of dose-escalation protocols.[51] Examples of models previously described that should be considered coupled with bone marrow reserve assessment include, in order of complexity:

1. Activity-based approach;
2. Total-body approach based on Equation 11;
3. Conventional blood-based red marrow dose approach (with or without blood sampling) based on Equation 7; or
4. Image-based approach based on Equation 2R (and Equations 1 and 3–5), employing a single representative regional marrow site, or multiple regional sites, and planar or SPECT imaging, to account for specific marrow activity uptake, if marrow targeting is involved.

A practical approach to establishing clinically meaningful dose-toxicity correlations would, thus, be to develop a model that included both absorbed dose (or activity, if justified based on comparison with the absorbed dose result) and reliable indicators of pretherapy bone marrow reserve, with the latter parameters either directly in the calculation to adjust model-calculated doses[5,41] or used indirectly by stratifying patients into clinically distinct subpopulations.[30,43,46] Baseline platelet counts, recent chemotherapy, and bone marrow involvement are reliable methods for assessing bone marrow reserve and have been shown to improve predictive dose-response relationships for myelotoxicity.[30,41,43,52,53] FLT3-L has recently been shown to be a better indicator of recovery of marrow progenitor cells and, thus, red marrow radiosensitivity for patients previously treated with cytotoxic therapy compared to peripheral blood counts.[5,54] Elevated FLT3-L plasma levels before RIT may indicate increased radiosensitivity of the bone marrow and, therefore, a higher degree of anticipated toxicity for a given model-calculated, radiation-absorbed dose.

A patient-stratification paradigm has been used in non-Hodgkin's lymphoma by only treating at the MTD, patients having an adequate bone marrow reserve (e.g., a baseline platelet count $\geq$150 K cells/mm^3) and a limited marrow involvement with disease ($\leq$25%).[30,43] Patients with platelet counts between 100 K and 150 K cells/mm^3 are treated with an attenuated dose and patients are excluded from treatment if their baseline platelet count is below 100 K. Treatment prescriptions based on the total-body dose or administered activity adjusted for body weight for the FDA-approved agents ^{131}I tositumomab and ^{90}Y ibritumomab tiuxetan, respectively, have demonstrated acceptable safety in these previously treated defined patient populations. Red marrow dose estimates (whether blood-based or the more appropriate image-based estimates) did not appear to provide a more meaningful treatment approach. Perhaps this was due to the requirement that all patients had limited marrow involvement with disease and that unlabeled antibody is administered before the radiolabeled antibody infusion. The treatment-prescription methods should be expected to work even better in *de novo* patient populations. In fact, in 76 previously untreated patients receiving ^{131}I tositumomab for the treatment of non-Hodgkin's lymphoma, grade 4 neutropenia occurred in 5% of patients and no patients experienced grade 4 thrombocytopenia.[55]

Adjustment of the radiation-absorbed dose by parameters indicative of marrow reserve/radiosensitivity may also lead to more reliable approaches for managing individual patients. For example, Juweid et al.[41] used a four-parameter equation to predict platelet toxicity grade. The parameters were: red marrow dose, baseline platelet counts, multiple bone and/or marrow metastases, and chemotherapy 3–6 months before RIT, as these were the significant factors affecting hematologic toxicity according to univariate and/or multivariate analyses. The dose-toxicity correlation was improved from $r = 0.49$ to $r = 0.69$ and, importantly, severe (grade 3 or 4) toxicity could be classified accurately in all cases. Using FLT3-L-adjusted red marrow and total-body radiation doses in patients with solid tumors, estimated using Equations 7 and 11, respectively, Siegel et al.[5] demonstrated significantly improved correlation with hematologic toxicity ($r = 0.86$). With FLT3-L adjustment, the administered activity per unit body weight exhibited a dose-toxicity correlation coefficient of 0.79. Some of these correlations may represent a practical upper limit; absorbed doses or adjusted administered activities

are generally correlated with peripheral blood count indicators of toxicity (using either percent decrease, grade, or nadir) which are not strictly linearly related to response except at low nadir levels (e.g., platelet nadirs of 45 and 90 K observed in 2 patients do not correspond to a factor of 2 difference in outcome for these patients). As an illustrative example, when patients were separated in terms of the severity of their bone marrow toxicity, those patient experiencing grade 0–2 platelet toxicity had a significantly reduced dose-toxicity correlation, compared to those patients exhibiting grade 3 or 4 toxicities.[5] Further, normal peripheral blood cell counts are typically considered as sufficient indicators of patient tolerance for additional myelosuppressive treatment. Peripheral blood counts, however, do not reliably predict patient response to myelosuppressive therapy. During the recovery period after cytotoxic chemotherapy, hematopoietic progenitor cells become mitotically active to replenish the bone-marrow compartment and remain hyperproliferative even after normalization of peripheral blood counts.[5,54] The FLT3-L-adjusted red marrow dose-enabled determination, with 93.3% accuracy, of which patients experienced grade 3 or higher myelosuppression and which patients experienced grade 0–2 toxicity. All patients experiencing grade 3 or higher toxicity were accurately identified.

These retrospective data analyses incorporating absorbed-dose adjustment by indicators of bone-marrow reserve appear to represent a more predictive dosing model. Because FLT3-L has only been shown to be a useful biologic marker to gauge bone-marrow tolerance and thereby provide a meaningful predictive model of toxicity, the model would require evaluation in a phase I or II safety-efficacy clinical trial to apply this knowledge to adjusting the treatment prescription. Further work needs to be done to explore whether the findings with FLT3-L in solid tumors are applicable in other tumors (e.g., lymphomas) or if other thrombopoietic cytokines would be useful.

CONCLUSION

Treatment planning for individual patients based upon tracer radiation dosimetry is an attractive concept and is an opportunity for targeted radiotherapy.[56] In previously untreated patient populations, such as the case in thyroid cancer treatment with $Na^{131}I$ or targeted radiotherapy if employed as a frontline therapy, dosimetry on its own may play an important role. Given the heavily pretreated patient populations generally receiving RIT in a nonmyeloablative setting, it is almost certain that model-calculated doses would require modification by factors indicative of bone-marrow status. In these patients, dosimetric approaches coupled with a reliable pretherapy assessment of bone-marrow reserve and radiosensitivity, should be able to establish clinically meaningful predictive models of hematologic toxicity. This may lead to better treatment planning by allowing for a more patient-specific therapeutic dose administration intended to optimize treatment efficacy and minimize severe hematologic toxicity. Models may vary, depending upon their applicability for a particular radiolabeled antibody treatment in a given patient population.

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