Toward Patient-Friendly Cell-Level Dosimetry

Dosimetry for targeted radionuclide therapy is a relatively young field. Although initial work can be traced back to the late 1940s (*1*), the MIRD Committee formalism that forms the foundation for most current approaches was published in the mid 1970s (*2*), and the drive for improved dosimetry to meet the requirements of targeted radionuclide therapy did not begin until the 1980s. During this period, the absorbed fraction and S value tables of MIRD Pamphlet 11 (*3*) and subsequently the values published by Cristy, Eckerman, and Stabin (*4,5*) and implemented in the software package MIRDOSE3 (*6*) formed the basis for almost all dosimetry calculations.

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These data are traditionally characterized as making up the physics portion of the absorbed dose calculation; that is, they enable the conversion of the total number of radionuclide transformations in a particular source tissue to absorbed dose in a target tissue. Such a conversion requires information on the emission properties of the radionuclide as well as the source–target tissue anatomy and composition. Given an appropriate model of human anatomy and composition, Monte Carlo calculations that track energy deposition events to different target regions from emissions in one or more source regions are used to generate photon or electron absorbed fractions for different source–target combinations, and these data are then used to generate radionuclide S values. These components are considered removed from the more difficult and messy biologic problem of determining the radiopharmaceutical kinetics needed to estimate the total number of radionuclide transformations in source tissues. Much of the effort in improving clinical radionuclide dosimetry over the past 10 y has focused on the biologic part—establishing more accurate methods for collecting radiopharmaceutical kinetics, in vivo. These efforts have led to surrogate measures of pharmacokinetics (*7,8*) and also to improved image quantitation methodologies tailored toward the radionuclides used in targeted radionuclide therapy (*9–13*).

Until recently, less attention had been paid to improving the physics input portion of the dose calculation method. Improvements in this area require more detailed anatomic models, both at the macroscopic level and at the microscopic level, and also improved Monte Carlo techniques. The need for such improvements has been greatest for the red bone marrow. The red bone marrow is the dose-limiting organ in the majority of targeted radionuclide therapy. As has been previously reviewed (*14,15*), the anatomic data used to generate the red marrow S values for the adult male of Pamphlet 11 and MIRDOSE3 came from a single 44-y-old man (*16,17*). Because the marrow mass was not available from this subject, the masses used to convert the absorbed fractions to S values came from studies dating to 1926 (*18,19*). Also, because the absorbed fractions were calculated on the basis of measured chord-length distributions, the loss of energy to cortical bone from energetic β-emitters such as ^{90}Y could not be directly modeled, nor could be the reduction in marrow dose due to the variable fraction of hematopoietic tissue taken up by adipocytes (i.e., cellularity).

Fortunately, primarily because of the outstanding work of the University of Florida group, the state of affairs in marrow dosimetry has vastly improved over the past 2–3 y. This group has generated consistent anatomic models of the marrow on a macroscopic and cellular scale and has used these to perform 3-dimensional cell-level electron transport for several trabecular bone regions (*20,21*). These models have been used to generate absorbed fractions that account for energy loss to cortical bone and also for marrow cellularity (*22–24*).

The paper in this issue of *The Journal of Nuclear Medicine* by Watchman et al. (*25*) adds to this group's already impressive contributions to this area. The article provides the basic data and describes a formalism for taking a step toward cell-level dosimetry while remaining within the overall MIRD S value formalism. As a step toward adjusting the mean absorbed dose to trabecular active marrow so as to account for the possibly nonuniform distribution of target cells, the distance between the trabecular bone surface and hematopoietic stem and progenitor cells and also their distance from blood vessels was measured by digital image analysis of immunohistochemically stained human bone marrow slides. The analysis showed an inverse linear relationship between distance from the trabecular bone surface and hematopoietic stem and progenitor cell density. In other words, the relevant target cells for hematopoietic suppression are not uniformly distributed throughout the marrow cavity but rather are concentrated close to the trabecular bone surface. Likewise, blood vessels were found more frequently near trabecular bone surfaces but with an exponential,

Received Nov. 3, 2006; revision accepted Nov. 9, 2006.
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DOI: 10.2967/jnumed.106.036749

rather than a linear, drop with distance from the bone surface. Another interesting observation was that the distance between blood vessels and hematopoietic stem and progenitor cells is lognormally distributed, meaning, as the authors point out, that there is a shared spatial niche between these 2 components of the bone marrow. The authors go on to show how these data could be used to scale bone marrow S values (e.g., trabecular bone surface source irradiating trabecular active marrow) to weight the estimated absorbed dose according to the spatial distribution of the relevant target cell population.

The objective of dosimetry in targeted radionuclide therapy is to provide information that will help improve patient care. With this objective, estimated absorbed dose is useful to the extent that it relates to response. The move from mean absorbed dose over an organ volume to an absorbed dose that is weighted to account for the spatial distribution of the relevant target cells is an important step in this direction, but more is needed. The conceptual 2-component framework of radionuclide dosimetry, requiring the physics of calculating absorbed fractions and S values and the biology of determining the number of radionuclide transformations, must evolve to a 3-component framework that would take the resulting physics quantity absorbed dose and incorporate a third conceptual component, the radiobiologic modeling required to translate absorbed dose to biologic effect (*26*).

The translation of model and methodologic improvements to the clinic will require additional patient data. The sophisticated tools will not be useful if the input data required to apply them cannot be obtained or can be obtainable only at substantial logistic and monetary cost. This is perhaps the biggest challenge in the development of advanced dosimetric methods. Because of the costs, clinical implementation cannot be justified without an evaluation of the benefits. Benefits cannot be assessed unless the methodologies are widely implemented. With advances in technology, a focus on innovative approaches to find simpler data collection methods, the use of preclinical and postmortem studies, and knowledge gained from developments in external radiotherapy, we will surely find our way out of this catch-22.

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