

# $\alpha$ -Particle Emitters in Radioimmunotherapy: New and Welcome Challenges to Medical Internal Dosimetry

Over the past decade, there has been progressively stronger interest in the use of  $\alpha$ -particle emitters for radioimmunotherapy (1–6). With proper localization of the labeled antibody, the high linear energy transfer of  $\alpha$ -particles provides a correspondingly high probability of mitotic cell kill when compared with an equivalent number of cellular traversals by lower linear energy transfer  $\beta$ -particles. Consequently, much developmental work has been initiated in the production, chemistry, and preclinical trials of candidates for radioimmunotherapy such as  $^{211}\text{At}$ ,  $^{212}\text{Bi}$ ,  $^{212}\text{Pb}$ ,  $^{225}\text{Ac}$ ,  $^{213}\text{Bi}$ , and  $^{223}\text{Ra}$  (7). In general,  $\alpha$ -emitters with half-lives that are either relatively short or relatively long compared with transient times in blood as well as diffusion and binding times in disease tissues may be considered. Those  $\alpha$ -emitters with relatively short half-lives, such as  $^{213}\text{Bi}$ , will most likely be restricted in their application to small, readily accessible tumors. For treatment of larger solid tumors, longer-lived  $\alpha$ -emitters such as  $^{225}\text{Ac}$  and  $^{223}\text{Ra}$  can also be considered. However, longer-lived radionuclides require more extensive normal organ dosimetry and biokinetics of their multiple unstable daughters in evaluating clinical efficacy. With high probability, the recoil energy of the  $\alpha$ -emission will result in destruction of their chemical bonds with the antibody, re-

sulting in the release of the daughter as a free element.

Two very different approaches can be applied to the dosimetry of  $\alpha$ -particle emitters. One is microdosimetry, in which the probabilistic nature of  $\alpha$ -particle emission and its trajectory through the cell and cell nucleus are explicitly considered (1,8–10). In a microdosimetric analysis, probability density functions of specific energy are obtained (stochastic expressions of energy imparted per unit mass to small targets), as well as frequencies of zero-dose contribution. Input data for such an analysis, however, require detailed knowledge of geometric features such as the spatial distribution and size of the source and target regions (e.g., cellular and nuclear sizes and subcellular distribution of the radionuclide). Meaningful correlations to biologic response further require data on the timing of the decays within the phases of the cell cycle and the variations of cellular radiosensitivity during these phases. In many cases, such data are not available in the clinical setting.

A simpler approach is to extend the MIRD schema to the cellular level and estimate mean absorbed dose to the cells or cell nuclei through the application of cellular S values. In its 1997 monograph, the MIRD committee published extensive tables of cellular S values for a wide range of  $\alpha$ - and  $\beta$ -emitting radionuclides (11). These tabulations include S values for the cell and cell nucleus as target regions and for the cell, the cell surface, the nucleus, and the cytoplasm as potential source regions.

In this issue of *The Journal of Nuclear Medicine*, Hamacher et al. (12) have provided an elegant extension of

the cellular S value methodology to include time-dependent partial contributions of the various daughter emissions in the serial decay chains of  $^{225}\text{Ac}$ ,  $^{221}\text{At}$ ,  $^{213}\text{Bi}$ , and  $^{223}\text{Ra}$ . In their approach, a cutoff time ( $\tau_0$ ) is selected before which free elemental daughter radionuclides are considered to remain in the same source configuration as that assumed for the parent. At short cutoff times, the daughter radionuclides, which are released as free elements after the  $\alpha$ -decay of the parent, diffuse or migrate far from the site of the parent decay and thus the cellular target dose results only from the decay of the parent. The authors note that for parent decays in blood circulation, short values of  $\tau_0$  are applicable. For tumor interstitium, intermediate values of  $\tau_0$  would be appropriate; thus, the total cellular dose is contributed by the parent and a  $\tau_0$ -dependent fraction of the cumulative decays of the daughters of the serial decay chain. It is clear that this approach to cellular dosimetry lends itself nicely to broader considerations of the biokinetics and dosimetry of radionuclides with multiple unstable daughters as proposed under a matrix formalism developed by these same authors.

Several issues and challenges of  $\alpha$ -particle dosimetry are highlighted through this approach. First, what value of  $\tau_0$  is appropriate and under what conditions of the cellular microenvironment? What is the spatial mobility of these daughter radionuclides within tissues and cellular microenvironment that would permit quantitative selections of  $\tau_0$ ? To correctly perform this analysis, detailed knowledge of the chemical diffusion coefficients for each elemental species within various

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tissue compartments (e.g., nucleoplasm/cytoplasm, extracellular fluid, cellular membranes, bone marrow) would be needed. In most cases, such details for high-Z elements are not available. It is for this reason that the International Commission on Radiological Protection (ICRP), in its publication 30 (13), makes the simplifying assumption that “daughter radionuclides produced from their parent within the body stay with and behave metabolically like their parent.” Only in the case of incorporated radium are the longer-lived radon daughter radioisotopes considered to have an independent biodistribution within the ICRP 30 framework. Clearly, research in the area of intratissue mobility of high-Z elements would be of great utility both to radionuclide therapy and to internal dosimetry for radiation protection considerations.

Second, the tabulations of cellular S values implicitly consider only the mean self-dose from activity originally bound to the target cell. As an unstable daughter is released from its parent decay site, it will diffuse further and further away from the original target cell. The dose contribution to the target cell for each daughter emission would then abruptly transition to zero, as assumed here, and would decrease continuously with increasing distance from the cell. For a higher energy  $\alpha$ , the dose to the cell nucleus might initially increase as the Bragg peak of the  $\alpha$ -ionization track is brought inside the cell nucleus. Also, as the unstable daughters migrate away from the target cell, they will increase their dose contributions to neighboring cells. In fact, a further extension of the cellular S value methodology should consider multicellular clusters of cells (14). However, this improved and more realistic geometry of the parent and daughter source–target geometry will necessarily require more detailed information on daughter mobility and activity distributions throughout the cluster.

Third, in their matrix formalism for multiple unstable daughters, the authors also consider the dose to normal

organs as required in the evaluation of the clinical efficacy of these  $\alpha$ -emitting radionuclides for radioimmunotherapy (15). A compartmental analysis of activity in normal organs might include separate determinations of the cumulative decays within the parenchymal tissues of the organ (incorporated activity), and the cumulative decays within the vascular content of the organ (activity in transit through the organ). For photons and even high-energy  $\beta$ -particles, emissions within the larger to intermediate blood vessels of an organ are considered to contribute to the overall mean organ dose. For short-range  $\alpha$ -particles, however, many of the blood source decays would yield energy deposition events restricted to the vessel lumen (blood and blood elements) and thus make no contribution to the parenchymal tissue dose. This fact motivates one to reconsider traditional models of normal organs as are used in the MIRD and ICRP methodologies. Potential improvements in organ dosimetry would then require organ models in which larger vessels are explicitly delineated. This can be challenging in the context of geometric, stylized models of organs. With newer developments in tomographic computational models, perhaps such intraorgan tissue and vasculature differentiation may be feasible (16,17).

Finally,  $\alpha$ -particle dosimetry directly challenges the MIRD schema in that, historically, the final quantity of interest has always been absorbed dose. Differences in biologic response after equivalent energy deposition by photons/ $\beta$ -particles and  $\alpha$ -particles obviously require scaling of the absorbed dose to arrive at a biologically equivalent dose quantity. Here, one may initially look to radiation protection quantities such as the dose equivalent and the equivalent dose, in which quality factors and radiation weighting factors, respectively, are applied (18,19). In radionuclide therapy, however, this approach is not ideal, as values of Q and  $w_R$  have been proposed primarily with prospective dose assessment in mind and only considering stochastic biologic effects. In many cases, medical

therapy utilizes dosimetry as a predictive tool for more near-term deterministic effects. With this in mind, the ICRP recommendations for target tissue definitions cannot always be used. For example, the ICRP methodology for skeletal dosimetry focuses on endosteum and marrow stem cells as the relevant targets in radiation protection. In radionuclide therapy, however, these tissues might not be the only relevant targets within the skeleton when predicting near-term marrow toxicity.

Where does this leave us? Is the increased interest in  $\alpha$ -emitters in radionuclide therapy providing technical challenges to medical dosimetry that are intractable? They might be if medical dosimetry continues to rely solely on the physics of energy deposition and geometric formulations of source and target regions, even if treated stochastically through microdosimetry. The use of  $\alpha$ -emitters provides the perfect stimulus to the medical dosimetry community to fully embrace new advances in molecular biology and in vivo microimaging and to redefine and expand its role and function as it seeks improved methods for predicting biologic response.

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