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EDITORIAL

The Importance of Accurate Radiation Dosimetry in Radioimmunotherapy of Cancer

The ultimate objective of radiation dosimetry in the treatment of cancer is to predict the biologic effects of energy deposited in tissue, thus allowing a physician to prescribe therapy that will benefit a patient with cancer. The role of the dosimetrist is well established in conventional radiation therapy, where there are established methods for performing dosimetric estimation and measurement, and for interpreting and applying the results to experimental and clinical cancer therapy. The role, value and methodology of radiation dosimetry in radioimmunotherapy is less well established. Although there have been efforts to standardize estimation of radiation dose in humans (*1,2*), optimal, uniform methods for dosimetric estimation and measurement, and interpretation of radiation dose, have not been commonly accepted. Dosimetric techniques suitable for application in therapeutic animal studies are even less well formulated.

In radioimmunotherapy, radiation energy is imparted at a low dose rate to tissues from internally distributed sources. Thus, the estimation of deposited radiation dose and its interpretation, will differ significantly from external radiation therapy. The total amount and rate of energy deposition in individual tissues varies by tissue and is determined by the biodistribution of the administered radionuclide and the physical characteristics of emitted particles. Biodistribution will depend on a multitude of factors, including the specificity and amount of the carrier molecule infused, the radionuclide and chemistry of conjugation to the carrier molecule, and the total amount of conjugate administered. Since radiation energy is deposited over a prolonged period, i.e., hours to days, it may be necessary to take into account any early biologic effects resulting from the radiation which might influence late biodistribution (*3*) or from associated combined modality therapy (*4*).

Once biodistribution is known, accurate estimation of absorbed radiation dose in a particular tissue will depend upon a dosimetric model that includes both the physical characteristics of the emitted particles and the specific spatial and temporal distribution of the source radionuclide compared to the target tissue. Techniques for correlating absorbed dose to biological effect, and utilizing dose estimates for extrapolating from experimental models to human patients, are still being developed. The study of Hosono et al. (*5*) exemplifies the unresolved and evolving nature of dosimetric estimation and its clinical application in radioimmunotherapy.

In the accompanying manuscript, Hosono et al. present data showing that infusion of an ^{131}I-labeled antibody, NE150, which binds to the NCAM molecule present on small cell lung cancer, can produce a greater therapeutic effect than an equivalent amount of an ^{131}I-labeled antibody that does not bind to tumor. The toxicity of this therapy is defined. Efficacy and toxicity data are accompanied by an estimate of radiation dose to the tumor and normal tissues. The authors hope that correlation of these two datasets will provide a means of comparing these results to those of other investigators, predicting the radiation dose required to produce an anti-tumor effect and the toxicity associated with therapy, and extrapolating the results in animal models to the clinical situation. How well do the techniques used by Hosono et al. (and historically by many other investigators, including ourselves) meet these objectives?

Successful interpretation of experimental studies on the effects of radiolabeled antibodies in cancer treatment requires a careful analysis of the biological distribution of the administered radionuclide in normal organs and tissues of the body, in tumors, and in circulating blood. This may be accomplished by serially sacrificing different groups of laboratory animals at several time points after the initial injection of radiolabeled antibody, and determining the amount of radionuclide in each of the major organs, tumors, and blood. The biokinetics of the radionuclide may then be evaluated for each tissue by evaluating the concentration of activity (μCi or Bq per gram) in each tissue over time through complete decay (infinite time). When the time-dependent concentrations of the radionuclide in individual tissues are known, further assessments may be made to determine cumulated activities and radiation absorbed doses.

Investigators usually decay-correct the tissue-count data with an appropriate counting standard to infer the concentration of the antibody in tissue with time. This is commonly referred

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to as a measure of the "biological" retention of the (cold) antibody. However, radiation dose is related to the "not decay-corrected," or "effective" retention of activity in tissues, reflecting both radioactive decay and biological clearance processes. Although this concept seems simple, countless professionals have confused "biological" data with "effective" data in dose assessment.

Biodistribution data for dosimetry estimates are presented by Hosono et al. (*5*). An important detail in interpreting these data is the fact that biodistribution was directly determined in mice receiving a therapeutic amount of radiolabeled antibody, rather than by extrapolation from the biodistribution of trace-labeled antibody. As shown in their Figure 1, there were very significant differences in tumor volume between mice receiving trace labeled antibody, whose tumors grew exponentially, and those receiving a therapeutic dose, whose tumors regressed. Since these changes were occurring over the first three weeks (the time period over which antibody was accumulating in tumor), it seems unlikely that antibody uptake and retention would be identical in the two situations. Because the data were obtained in a therapeutic setting, we can be comfortable that the data used for dosimetric estimates accurately reflect biodistribution in mice followed for tumor response. However, it is not clear from the text whether the values presented represent "biological" retention or "effective" retention and it must be assumed that the correct values were used for the dosimetry estimates.

The radiation absorbed dose is related to the cumulated activity in a specific tissue. For several reasons, however, dose is not directly proportional to cumulated activity. Early pioneers in medical internal radiation dosimetry recognized that some of the energy (usually as penetrating gamma rays) emitted from radionuclides in a human organ or tissue may be imparted to more distant organs, or may completely escape the body. The mathematical methods recommended by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine were originally developed with the thought of fully accounting for the absorbed fraction of gamma energy that could be assigned to each organ or tissue, considering the source organ from which the radiations were emitted (*6,7*).

For convenience, the MIRD absorbed fraction for beta particles was assumed to be 1.0, and beta-particle cross-irradiation of organs was disregarded as an insignificant contributor to total organ dose. This is a proper assumption for the large organs of the human. However, ranges of beta particles are important considerations for the small organs of the mouse. Small organs containing radioactive material irradiate adjacent tissues, and those adjacent tissues, in turn, irradiate other adjoining organs. The degree of cross-organ irradiation depends on the energy of the emitted radiation and its spatial distribution within the source tissue.

The cross-organ energy deposited may be a small fraction of the total energy emitted from activity residing in the source organ (in the case of ^{131}I), or a larger fraction of the total (in the case of ^{90}Y), depending on organ size, shape, and relative surface area. Relative differences in organ activity concentrations also determine the importance of cross-organ dose contributions.

Hui et al. (*8*) recently developed a MIRD-style approach for calculating beta cross-organ doses in the laboratory mouse. Their approach assessed the beta absorbed fraction in small organs, tumors, marrow tissue, and the remainder tissues of the mouse using integrations on Berger point kernels (*9*). This approach provides beta cross-organ dose contributions, and accounts for the effects of changes in target tissue mass over time on the total absorbed dose. Hui et al. showed that the self-organ absorbed fractions for ^{90}Y beta particles in the mouse ranged from 15% to 20% in smaller organs (marrow and thyroid) to 65%–70% in larger organs (liver and small intestines). Although the cross-organ beta dose is not as significant for ^{131}I as it is for ^{90}Y, ignorance of the beta absorbed fraction may lead to significant errors in estimates of doses to small tissues, such as tumor implants.

Beatty et al. (*10*) applied the computational mouse model to data from nude mice bearing CEA-expressing WiDr human colon cancer xenografts injected with ^{90}Y-anti-CEA monoclonal antibody to calculate absorbed doses to various tissues and tumors. They found that such an approach more accurately accounts for self-organ absorbed and cross-organ absorbed doses, and allows a more accurate estimation of radiation doses to tumor and critical organs such as the marrow, spleen, lungs, and kidneys. Ugur et al. (*11*) applied the same mouse model to ^{131}I-labeled monoclonal antibodies in mice and showed differences between calculated absorbed doses and doses measured using implanted calcium sulfate:dysprosium thermoluminescent dosimeters.

Of importance to accurate absorbed dose calculations in the mouse are the size and shape of the organ, the density and atomic composition of the tissue (i.e., lungs compared to liver and bone) and the spatial distribution of the radioactive sources. In other words, cumulated activity in a source organ alone is not adequate for accurate radiation dosimetry, and the effect of density on absorption of energy in tissue must be determined. Accurate estimation of tumor doses in a successful therapeutic study becomes even more problematic. As the authors note, the tumor volume changes over the same time course as radiation is being deposited and can rapidly approach a very small residual. The extent to which such factors will influence absorbed dose will vary with radionuclide, but may be substantial (even for ^{131}I).

The article by Hosono et al. (*5*) takes a traditional approach to beta dosimetry in the small organs of the mouse and neglects the finer aspects of radiation dosimetry in small organs. We cannot determine from the article whether the Berger point kernels have been integrated over target-organ vol-

umes and whether the rapid growth or degradation of tumor volumes with therapy have been taken into account. The authors recognize that radioactivity in the blood "might contribute to" irradiation of the lungs and other tissues, but do not assess those contributions. The absence of this information makes it difficult to compare the current dose estimates to those of others, particularly for therapy with other radionuclides (*12*).

Future research with radiolabeled monoclonal antibodies should use appropriate methods and models so that accurate doses are reported and experimental results are more appropriately extrapolated to clinical situations. Improved immunoconjugates will be developed and tested in small animals, such as the nude mouse. This work will involve continuously reevaluating each of the many factors influencing the localization and retention of radiolabeled antibodies. Radiation absorbed doses to both tumors and normal organs will need to be assessed with improved accuracy for evaluating therapeutic ratios and the effectiveness of the administered activity.

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