Improving Insight into Radiobiology and Radionuclide Therapy

In 1969, Edith Quimby, ScD, one of the founders of modern radionuclide dosimetry, concluded her presentation at an Atomic Energy Commission symposium at the Oak Ridge Associated Universities entitled “Medical Radionuclides: Radiation Dose and Effects” with the statement: “Radionuclide dosimetry is not a finished product, but it has come a long way from the early empiric days. We must be grateful to the patient people who have spent untold hours on these developments.” (1).

Thirty-five years later, this statement is still relevant. It has been confirmed by the efforts of Marion de Jong et al. from The Netherlands, as reported on pages 1168–1171 of this issue of The Journal of Nuclear Medicine (2). de Jong et al. have convincingly demonstrated that, in radionuclide dosimetry, it is not valid to assume a uniform distribution of radiation sources in a target organ and, hence, that it is not appropriate to compare radiation effects from absorbed doses delivered by external-beam sources with doses from injected radionuclides.

The radiation-absorbed dose to the kidneys is a particular problem in the clinical assessment of peptide-based targeted radionuclide therapy of islet cell adenocarcinoma, malignant carcinoid tumors, and other somatostatin-receptor–positive tumors. The fraction of an injected dose of radiolabeled peptide retained in the kidneys can be reduced by amino acid infusions when a labeled peptide or antibody fragment has been administered. This practice is now standard in clinical protocols evaluating radiolabeled somatostatin analogs as therapeutic agents. The logic behind this approach is to inhibit reabsorption of the radiolabeled peptide that appears in the glomerular filtrate by administering comparatively large quantities of similar nonlabeled compounds.

In kidneys removed from 3 patients with primary renal tumors, de Jong et al. (2) have demonstrated by autoradiography a nonuniform distribution pattern for the radiolabeled peptide. The radiolabel is deposited in linear bands, most prominently in the inner renal cortex and also in the renal medulla. Unfortunately, de Jong’s group has not yet analyzed the precise histologic distribution on companion sections stained with hematoxylin and eosin, but the autoradiographs demonstrate the highest deposition of radionuclide in a well-defined pattern that is sure to correlate with specific structures. Although drawing conclusions would be premature, I find the pattern quite suggestive of deposition in the proximal and perhaps distal convoluted tubules. The proximal convoluted tubule is the site of reabsorption of amino acids from the glomerular filtrate and, so, is likely also the site of reabsorption of a small peptidelike octreotide and other somatostatin analogs.

Accurate demonstration of the precise localization of the site of reabsorption may assist in identifying drugs or other compounds that would be more effective in blocking or inhibiting the tubular reabsorption and subsequent deposition of the radiolabel.

Even while de Jong et al. (2) and others (3–5) have been trying to better relate the renal radiation-absorbed dose, as it is currently measured, to nephrotoxicity from 90Y-labeled peptide therapy and to take measures to reduce that dose, the Rotterdam group has been trying also to determine the relative therapeutic merits and potential toxicity of 90Y and 177Lu as labels for therapeutic uses (6).

It is desirable from a scientific, didactic, and clinical perspective to understand the relationship between the physical properties (physical half-life, type of emission, and energy of emission) of a radionuclide and the radiobiologic response elicited. This issue goes beyond the specific application of radiolabeled peptides in the treatment of neuroendocrine tumors. Currently, the nuclear medicine community has available 2 radiolabeled antibodies approved by the U.S. Food and Drug Administration for the treatment of non-Hodgkin’s lymphoma, one labeled with 90Y and the other with 131I. At this time, there has not been a randomized comparison of the 2 agents. Given the numerous variables in patient selection, one wonders if a clinical trial will resolve the question of therapeutic superiority. My own group has been evaluating the relative merits of 90Y- and 177Lu-labeled monoclonal antibodies in the therapy of metastatic prostatic cancer (7).

The observations and subsequent discussion of de Jong et al. (2) reinforce the notion that one must consider microdosimetry in order to understand the radiobiology of antitumor effects and organ or tissue toxicity. The early Quimby–Marinelli formulation and the subsequent MIRD formulation enable us to determine the radiation-absorbed dose to organs and tissues independent of the radionuclide. These formulations account for differences in the administered dose, the physical and biologic half-life of the different radionuclides, and the specific type and energy of the emission after each nuclear disintegration. The MIRD formulation also incorporates Monte Carlo statistics to further rationalize the randomness of the radiation emission and the distance and direction between a source and target organ or tissue. Nevertheless, compared with the absorbed dose for uniform external-beam radiation therapy, the overall radiation-absorbed dose calculated for radionuclide therapy often does not correlate with the therapeutic or toxic effects observed.
Questions remain about the differences in therapeutic and toxic effects from different radionuclides despite administration of similar radiation-absorbed doses.

Are these differences due to dose rate effects? This possibility was enthusiastically considered a few years ago, when the radionuclide therapy of painful bone metastases was attracting attention. Because clinical trials vary so much in patient demographics, it was desirable to identify a scientific basis for selection among the several radionuclides ($^{89}$Sr, $^{153}$Sm, $^{166}$Re, and $^{87}$Sn) available for clinical trials. To date, no convincing evidence exists that differences in the physical half-lives of these radionuclides have an impact.

Several years ago, O’Donoghue et al. determined the optimal tumor cure diameter (lethal dose delivered) as a function of β-particle energy (8). They demonstrated that lower-energy emitters are more appropriate for the treatment of micrometastases, whereas higher-energy β-emissions are less effective in that situation. Given that β-labeled carriers (peptides and monoclonal antibodies) cannot be assumed to be uniformly distributed, higher-energy radionuclides may be more effective in larger tumors. Bardies and Chatal (9) have calculated the absorbed fraction for β-emissions of different energies as a function of sphere diameter.

We must be grateful to Marion de Jong et al., because their observation of histopathologic differences in distribution of the radiolabel within an organ or tissue refocuses the spotlight on differences between radionuclides in terms of pathlength and linear energy deposition, both functions of the energy of the specific emission. Until now, in Quimby–Marinelli and MIRD formulations, in contrast to γ-radiation and x-rays (penetrating radiation), we have assigned a uniform absorbed-fraction value to all nonpenetrating radiation (α, β, and Auger). If the source and target were the same, it was assumed that 100% of the energy from nonpenetrating emissions was absorbed (absorbed fraction = 1.0); if the target was distant from the source, absorbed fraction was assigned a value of 0. It seems more appropriate now to consider the distribution of energy deposited over the pathlength of an emitted particle on a microscopic scale (even as we have done on a larger scale for γ-radiation) and to relate this distribution to the histopathology for tumors and normal tissues in order to determine the effective radiation-absorbed dose on a microscopic anatomic level.

To understand the relationship between radiation-absorbed dose and radiobiologic response in both tumors and normal tissues and organs, we must determine the microdosimetry; that is, we need to know the pattern of distribution of the radionuclide and account for the distribution of energy deposition on a microscopic and histopathologic scale. It is appropriate to repeat Dr. Quimby’s summation: “Radionuclide dosimetry is not a finished product, but it has come a long way from the early empiric days. We must be grateful to the patient people who have spent untold hours on these developments.” (1).

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REFERENCES