INVITED COMMENTARY

PET Imaging for Planning Cancer Therapy

Radioimmunotherapy has been under way as a major field of research in nuclear medicine for nearly 20 y. However, advances have been slow, and only now can we expect the first commercial products for cancer therapy to soon become available. What have been the obstacles to this development? The agents themselves have variable and often low levels of tumor binding in vivo, and solid tumors are usually radioresistant. Technology for assessment of patient dosimetry estimates has not been consistent because of the difficulties in determining accurate concentrations of the radiotracers in normal and tumor tissues by quantitative imaging (*1*,*2*). Up to now, the choices have been to image and treat patients with ^{131}I or to use ^{111}In as a surrogate to estimate the biodistribution of ^{90}Y as the therapeutic radioisotope (*3*). In both situations, the errors in determining tissue radioisotope concentrations for input into dosimetry estimates for planning treatment and evaluating observed toxicity are variable and can be large. Only a few investigators have seriously attempted to validate these methods and apply the validated techniques to clinical situations (*4*). Accordingly, optimization of the clinical therapy protocols to deliver maximum tumor dose and the push to define normal tissue toxicity limits have not proceeded.

In our experience, study protocols that prospectively describe true treatment toxicity and efficacy in terms of reliable radiation absorbed doses to normal tissues and tumors are usually required at this stage. Radiolabeled antibody therapy will succeed when optimized quantitative imaging and techniques to estimate radiation absorbed dose are the basis for the treatment plan for every patient. At the center of this requirement is an accurate, reliable means of determining the tissue concentration of radiolabeled antibody.

In this issue of *The Journal of Nuclear Medicine*, Lee et al. (*5*) describe a murine colon cancer xenograft model for studying the biodistribution of an ^{124}I-CDR–grafted humanized monoclonal antibody. The radiolabeled antibody bound to tumor and cleared background well. The behavior of the antibody was nicely described by a compartmental model of whole-animal biodistribution. PET imaging of the ^{124}I-labeled antibody showed high-contrast images of radiolabel in the tumor xenograft, with little residual activity in other tissues. The study was meticulously performed and showed that the new antibody construct avidly binds to tumor and clears from background tissues, that ^{124}I can be used as a trace radiolabel to study the biodistribution of the antibody in tissue, and that images of a tumor xenograft in mice can be obtained using conventional PET methods. Lee et al. provide the foundation for resolving the next important obstacle to using radiolabeled antibody for planning treatment: accurate determination of the concentration of radioisotope in tumors and normal tissues at several times after infusion to obtain input data for use in estimating radiation dose.

The nuclear medicine oncology community shows keen interest in the use of high-energy β- and α-particle emitters for cancer therapy. The increasing number of dedicated PET devices in large practices is providing an impetus for the development of radiopharmaceuticals and the expansion of their use beyond ^{18}F-FDG PET imaging of cancer. Using PET to address the issue of tissue concentration of the therapeutic antibody or construct will be an important step toward conducting trials on the effectiveness of cancer treatment. However, several obstacles relating to the difficulty of accurately quantitating ^{124}I- and ^{86}Y-labeled antibodies remain to be overcome. The high frequency of high-energy single emissions from these radioisotopes poses problems with image resolution and quantitation for conventional PET devices. Several imaging physics groups are actively investigating these issues (*6*,*7*). This solid report on antibody biodistribution by Lee et al. (*5*) should also serve as a call from the radioimmunotherapists to the PET imaging physics community to concentrate on overcoming these physics issues in PET imaging.

Much is at stake as biomedical researchers progress enormously in understanding the biology of cancer. A related surge of interest in molecular imaging is occurring. This is a new field in which the time has come for nuclear medicine practitioners to begin translating biologic information into new imaging methods and treatment strategies for cancer. This process has been the strength of the field of nuclear medicine and should continue to be so in this new era of discovery. In addition to generating more accurate dosimetry input data for patient treatment, the use of PET with disease- or phenotype-specific radiopharmaceuticals will provide definite quantitative parameters for following the response to treatment and for documenting heterogeneity in the tumor and in response to treatment with specific agents throughout the course of the disease. Imaging accuracy and specificity can be used directly to redesign and refine both radiopharmaceutical-based and nonradioactive therapies. Use of positron-emitting radiolabels for new biologically active radiopharmaceuticals will provide insight into animal models of cancer, such

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as that described by Lee et al. (*5*), and will lead to human clinical trials. Well-designed prospective clinical trials are the next step after definitive studies on animal models. These areas of investigation are now close to being able to take advantage of the excellent image resolution and quantitative capabilities of PET.

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