INVITED COMMENTARY

How Far Have We Come with Solid (Nonhematologic) Tumor Radioimmunotherapy?

Twenty years ago, when phase I clinical trials began using a targeted approach to directing radioactivity toward cancer for diagnosis and therapy, the hope was that the management of cancer would soon change. The potential seemed enormous, that is, to be able to selectively target cancer cells while sparing normal organs because of the specificity of monoclonal antibodies, which could be developed easily. Terms such as ''magic bullets'' were coined for this approach. Unfortunately, not much has been magical about this approach for patients with carcinomas; it has been an ongoing struggle with one disappointing trial after another. Problems were identified soon after the early clinical radioimmunotherapy (RIT) trials were completed, and although some of these problems have been overcome, the goal of ''curing cancer'' with radiolabeled antibodies still seems distant.

Success in achieving significant remissions of more radiosensitive tumors, particularly in patients with non-Hodgkin's lymphoma (NHL), has encouraged investigators to continue working to achieve clinically significant responses in patients with carcinomas. In patients with NHL, complete response rates vary from 50% to 80%, particularly for high-dose studies in conjunction with myeloablation. Relatively few clinical trials of systemic RIT for carcinomas have been reported. The few tumor responses observed in phase I and II trials in patients with resistant, bulky disease are probably more than simply anecdotal and show proof of the concept of the technology. In these trials, toxicity of normal organs from circulating radiation limited the amount of radioactivity that could be administered. A fractionated dosing schedule has not been possible because of immunogenicity of the antibodies.

For successful RIT, an appropriate radionuclide must be selected and an appropriate antibody for the particular cancer type must be produced. The correct mass dose of antibody must be defined in preclinical or clinical studies so that the radioimmunoconjugate can be directed toward tumor tissues in sufficient quantities to produce a therapeutic effect. The radiosensitivity of tumor types varies, and the biologic effect of low–dose-rate irradiation is likely to be different from that of external beam radiation. Thus, the absorbed dose required to eradicate tumors likely varies and has not been reliably established for any tumor. Furthermore, the patients have usually undergone variable prior therapy with myelosuppressive agents. Thus, the bone marrow—the organ most susceptible to the damaging effects of radiation—may be compromised, so that obtaining reproducible information from dose escalation studies to predict safe doses for any particular patient may be difficult.

While producing an ideal antibody, that is, one that binds tightly to tumor cells and without reactivity to normal cells, has been difficult, finding a suitable radionuclide is a more defined task. Only a few β-emitting radionuclides can be readily produced in adequate quantities and are therefore available for RIT. Most studies have used ^{131}I, but more recently trials with ^{90}Y have been reported. The ideal half-life or energy of the radionuclide has not been defined, but until greater penetration of antibody into macroscopic tumors can be achieved, the physical characteristics of the radionuclide may be of secondary importance. Wessels and Rogus (*1*), in 1984, examined the physical characteristics of several β-emitting radionuclides in conjunction with known pharmacokinetics of antibodies and concluded that ^{186}Re may be an effective radionuclide for RIT. Recently, ^{186}Re compounds have received further attention as therapeutic agents for bone pain palliation and also for preventing restenosis of coronary vessels after percutaneous transluminal coronary angiography.

^{186}Re has a medium-energy β particle (maximum energy, 1.07 MeV). The half-life (3.7 d) is appropriate for RIT because the half-life is compatible with that of a circulating intact antibody, particularly with the slower clearing chimeric and humanized antibodies. The pathlength of ^{186}Re may be better suited to small-volume disease than to the bulky disease of most patients in phase I clinical trials, such as in the study of Colnot et al. (*2*) in this issue of *The Journal of Nuclear Medicine*. Stable linkage of ^{186}Re with an antibody using a preformed chelate was developed by Fritzberg et al. (*3*), and that basic method of radiolabeling an antibody with ^{186}Re was also used in this clinical trial. The first clinical trials with ^{186}Re as the radiotherapeutic agent were reported by my group in 1992 using an $F(ab)'_2$ fragment of a murine anticarcinoembryonic antigen antibody and an intact murine adenocarcinoma antibody (*4*). Rather than doing a therapy-planning study with ^{186}Re-antibody, my group evaluated ^{99m}Tc and ^{186}Re as a matched pair, that is, the ^{99m}Tc-radioimmunoconjugate was used to confirm antigenic expression of the

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tumor in patients before they received the ^{186}Re therapy. Also, the ^{99m}Tc study was used in an attempt to predict the radiation absorbed dose from the ^{186}Re for the anticarcinoembryonic antigen antibody study (*5*). ^{186}Re has a 137-keV photon, so quantitative data from the gamma camera was obtained from both radionuclides.

Colnot et al. (*2*) have reported a phase I RIT study in patients with head and neck squamous cell cancers (HNSCC). In this carefully designed trial, the investigators selected ^{186}Re as the radionuclide and conjugated it to the chimeric U36 antibody. U36 is an antibody that reacts with the v6 domain of CD44, which is expressed in several tumor types. The antibody reacts with 99% of HNSCC. Although HNSCC is a relatively radiosensitive tumor, deposition of radioactivity in the tumor target was insufficient to produce meaningful responses from RIT as administered in this study. The ^{186}Re-cU36 antibody had a prolonged circulation time: the mean blood elimination–phase half-life was 80 ± 37 h and the whole-body clearance half-life was 344 ± 164 h. This circulation time resulted in a low maximum tolerated dose (MTD) because of marrow toxicity. The MTD was only 1.0 GBq/m^2 ^{186}Re, and the next dose level (1.5 GBq/m^2) resulted in grade IV marrow suppression in 2 of 3 patients, with fatal infection in 1 patient.

The use of the chimeric form of this antibody did not lower the incidence of antiglobulin enough to enable fractionated or repetitive dosing. Human anti-chimeric antibody occurred in 40% of patients and occurred early—within 1 wk. The 2-mg dose of the diagnostic study was immunogenic enough to cause an antiglobulin response in some of the patients. Other investigators using chimeric antibodies have encountered similar problems in that immunogenicity was reduced, compared with the intact murine antibody, but was still present, and blood clearance was slower (*6*). As stated in the article of Colnot et al. (*2*), a future study will use humanized antibody. Humanization of monoclonal antibodies appears to have solved the immunogenicity problem for all practical purposes, but the circulating time is often even more prolonged, further limiting the single-administration MTD.

The fact that some antitumor effects were seen at the MTD found by Colnot et al. (*2*) does provide encouragement for the approach. Thus, they concluded that ^{186}Re-RIT may have a role in minimal residual disease or as adjuvant therapy for HNSCC. Studies comparing treatment of small and more bulky tumors have shown greater uptake in smaller tumors in preclinical studies and higher response rates for smaller tumors in both preclinical and clinical studies (*7*). However, the use of RIT as adjuvant therapy remains questionable. If the benefit of using a radiolabeled antibody is the cross-fire effect of nontargeted cells in close proximity to antigen-positive cells, then single cancerous cells are unlikely to benefit from the effects of radiation from a medium-energy β emitter bound to a single cell.

The article of Colnot et al. (*2*) is also of interest because a key issue in treatment is how to determine the dosage for an individual patient. Predicting the dosimetry from RIT before treatment is important and was addressed indirectly with the ^{99m}Tc imaging study.

Tumor heterogeneity (antigen expression and inhomogeneous blood supply) may limit antibody localization. Thus, the ability to exclude patients from unnecessary high-dose radiation treatment by screening with an imaging study is attractive. If antigen expression is not evident, as assessed by absence of localization of the radioimmunoconjugate, the patient does not proceed to receiving RIT.

Most studies that use ^{131}I as the therapeutic isotope include an imaging study with a tracer dose of ^{131}I for patient selection and for dosimetry planning (*8,9*). From the imaging or diagnostic study, the activity that achieves a specific radiation absorbed dose to a particular organ can be estimated. Thus, rather than escalating the administered activity on the basis of an empiric increase in dosage or body size, dose escalation can be based on estimates of radiation dose to the whole body, the bone marrow, or other normal organs (the last when stem cells or marrow has been harvested to overcome the problem of marrow toxicity). Once the acceptable absorbed dose to normal organs has been established, the tracer study is a guide to the maximum amount of radioactivity that can be safely administered.

For therapeutic radionuclides other than ^{131}I, rather than using the therapeutic radioisotope twice, matched pairs have been studied for predicting dosimetry with more readily available radioisotopes. These pairs include ^{111}In and ^{90}Y, ^{99m}Tc and ^{186}Re, and ^{99m}Tc and ^{188}Re. Reports with ^{111}In and ^{90}Y (*10–12*) assume that if serum and urine clearance of both radioimmunoconjugates is similar, and the tissue distribution in animal models is similar, then the biodistribution in all human organs and tumors is similar. No method short of biopsy can validate this claim because of the lack of photon emission of ^{90}Y, but the claim does appear to be a reasonable assumption for clinical studies. For the ^{99m}Tc–^{186}Re pair, γ emission of both tracers allows quantitation of the ^{186}Re as well as of the ^{99m}Tc. The limiting factor here is the short half-life of ^{99m}Tc. Using a 1.1-GBq dose, quantitation beyond 24 h is not possible, and even by 24 h the statistics are questionable. In our studies evaluating the use of ^{99m}Tc and ^{186}Re as a matched pair (*4,5*), ^{99m}Tc could not reliably predict the ^{186}Re dosimetry for a patient.

However, the article by Colnot et al. (*2*) does suggest that the matched-pair hypothesis is valid and may be useful in selecting dosages to administer based on marrow dose estimates. Although the necessity of having identical mass doses of antibody for the 2 studies has been proposed, the mass dose of ^{99m}Tc-cU36 was 2 mg and the mass dose of ^{186}Re-cU36 was 52 mg, indicating that this degree of mass difference did not account for altered pharmacokinetics. The study was designed to compare organ biodistribution qualitatively for 21 h. Although both sets of images looked similar (as was the case in our studies), no quantitation study was per-

formed to compare actual organ uptake, which we observed to be different. However, the pharmacokinetics up to 24 h were similar, and the correlation coefficient (0.94) for the area under the blood curve was strong. If the ^{111}In–^{90}Y studies are used for predictions based on pharmacokinetic similarities, perhaps the same can be done for ^{99m}Tc–^{186}Re studies. With the availability of γ emissions for both isotopes, the next step would be a quantitative ^{99m}Tc study to compare whole-body clearance and normal organ uptake at 20 h. If the clearance and uptake are similar, this information could be used to help determine dosages for patients. Although assessing the degree of tumor uptake to predict dosimetry is ideal, no correlation has yet been found between tumor absorbed dose and response to therapy. Thus, the lack of quantitative ^{99m}Tc data on tumor uptake in reality is not now a limitation. Furthermore, prediction of normal organ dose is more relevant for phase I clinical trials.

The correlation of marrow dose estimates with marrow toxicity reported by Colnot et al. (*2*) is among the best that have been reported. The variability of prior treatments and patient characteristics will prevent these correlation coefficients from being high, at least until factors such as prior treatments and age can be included in the analysis, as was recently attempted (*13*). The correlation of marrow dose with the ^{186}Re-labeled antibodies seems to be generally more reliable than correlations with ^{131}I-labeled antibodies (*14*). An advantage in the study of Colnot et al. was that 8 of 11 patients had not previously received myelotoxic therapy. With the prolonged serum clearance of the chimeric antibody, the contribution of whole-body activity is probably relatively minor, but if, in the next study, whole-body clearance of ^{99m}Tc is shown to be similar to that of ^{186}Re, perhaps the predictions of marrow dosimetry will be valuable for planning therapy, particularly for trials in which nonmyeloablative doses are to be administered. The high variability in clearance of this antibody between patients suggests that a pretherapy study to determine optimal dose is desirable.

Other recent reports on the use of ^{99m}Tc–Re matched pairs used ^{188}Re (*15,16*). A comparison of ^{99m}Tc antigranulocyte antibody anti-nonspecific cross-reacting antigen (NCA)-95 and ^{188}Re showed no biokinetics correlation in the whole body, marrow, spleen, or kidneys (*15*). The cause was thought to have been early in vivo instability of the ^{188}Re compared with the stable ^{99m}Tc but could not be shown in vitro. An abstract comparing ^{99m}Tc(V) dimercaptosuccinic acid (DMSA) distribution with ^{188}Re(V)DMSA showed a high correlation of tumor-to-background ratios after scatter correction of ^{188}Re images. This information was thought to be useful for therapy planning, that is, for assessing eligibility for palliation of bone pain (*16*). Recently, ^{99m}Tc-methylene diphosphonate (MDP) has been evaluated as a diagnostic agent for ^{166}Ho-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonate (DOTMP) to assess the level of skeletal localization of the ^{166}Ho-phosphate and predict the marrow dose for marrow ablation (*17*). Again, good correlation between the agents was found, but scatter correction of the bremsstrahlung radiation was necessary to improve the accuracy of quantitation for the predictions. This finding is encouraging, but the variable conclusions reached with these different studies suggest that each system must be evaluated separately, with, for correct comparisons, careful attention to details such as the mass of the components, the effect of circulating antigen on biodistribution, the ligand-to-radionuclide molar ratios in both preparations, and the accuracy of gamma camera quantitation.

In several situations, patient selection and dosimetry planning will continue to be important for RIT. These situations include studies in which antigen expression varies and not all patients or tumors express the antigen, and situations in which the pharmacokinetics are highly variable. Imaging studies that can select suitable patients and a suitable dose are a powerful tool for therapy. If radionuclides that are less costly and more readily available can be used, and if limited data are sufficient for predicting dose from the therapy administration, these studies will be more acceptable in the busy nuclear medicine department.

As these phase I studies continue, the use of smaller molecular constructs for improved penetration into the tumor is being assessed (*18,19*), as is the synergistic effect of RIT with chemotherapy (*20–22*). RIT may have a role by boosting radiation to the tumor in conjunction with other therapies. Other approaches with antibodies are being investigated, one of which is a pretargeted approach that avoids prolonged exposure of marrow to circulating radiation. This approach is being evaluated preclinically and in clinical trials using either bifunctional antibodies (*23,24*) or the avidin–biotin techniques (*25*). It may be particularly valuable when using humanized antibodies, in which marrow exposure from the prolonged circulation time is reduced.

Although RIT alone is not yet valuable for patients with solid tumors, the ongoing trials and their results provide new insights into this potentially useful treatment modality.

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