TECHNETROUBLES

TO THE EDITOR:
Molybdenum made in Peru'?
May replace Nordion, is it true?
The distance to Lima
causes decay in extrema
Will DOE ever come thru?

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Radiolabeled Antibodies as Cancer Therapeutics

TO THE EDITOR: The article by Sgouros (*1*) and the accompanying editorial (*2*) rekindle the enthusiasm for radiolabeled antibodies as cancer therapeutics, which was also the focus of another recent editorial in the *Journal* (*3*). The suggestion that controlling nontargeted vascular radioactivity to achieve higher tumor doses would be most effective in the therapy of micrometastatic disease is in fact supported by experimental results achieved in mice having lung metastases of human colon cancer, when given a well-tolerated dose of ^{131}I-labeled antibody to carcinoembryonic antigen (CEA) (*4*). A single injection of the specific antibody increased survival to over 22 wk, whereas the control animals died within 5–10 wk. More recently, it was found that the survival of animals with larger tumor nodules could be improved by treatment with radiolabeled antibodies, but death could not be prevented, whereas animals with micrometastatic disease could be cured (*5*). In contrast, treatment of these animals with metastases with a maximum tolerated, fractionated dose of 5-fluorouracil and leucovorin, the current method of choice for adjuvant treatment of colorectal cancer, failed to improve survival. Tumor dosimetry from patients given ^{131}I-labeled anti-CEA antibody has suggested that smaller tumors will receive a higher absorbed dose per millicurie than larger tumors, with 1-g tumors receiving as much as 200 cGy/mCi (*6*). These studies clearly support the views communicated by Sgouros and by Zanzonico and encourage the investigation of radioimmunotherapy in an adjuvant setting. However, many issues and potential obstacles remain to be resolved, such as single versus divided doses, increasing the percent uptake, intact IgG versus fragments, humanized versus human forms, role of vasculature, use of plasmapheresis, second antibody or other methods designed to reduce blood-pool activity, etc. The problems are further appreciated when one considers the dynamics of targeting micrometastases when a concomitant larger mass is present (*7*). In the same micrometastasis model, the survival of animals was greatly reduced if treatment occurred when there was a larger tumor mass present. The larger tumor reduced the total amount of radioantibody accreted in the micrometastatic colonies, thereby decreasing the therapeutic effect.

Thus, these preclinical studies support the view that radiolabeled antibodies ultimately will play a role in the treatment of cancer, most likely as an adjuvant for therapy of micrometastatic, solid tumors and of radiation-sensitive neoplasms, such as lymphoma (*3*).

REFERENCES

1. Sgouros G. Plasmapheresis in radioimmunotherapy of micrometastasis: a mathematical modeling and dosimetrical analysis. *J Nucl Med* 1992;33: 2167–2179.
2. Zanzonico P. Radioimmunotherapy of micrometastases: a continuing evolution [Editorial]. *J Nucl Med* 1992;33:2180–2183.
3. Goldenberg DM, Griffiths GL. Radioimmunotherapy of cancer: arming the missiles. *J Nucl Med* 1992;33:1110–1112.
4. Sharkey RM, Weadock KS, Natale A, et al. Successful radioimmunotherapy for lung metastases of human colonic cancer in nude mice. *J Natl Cancer Inst* 1991;83:627–632.
5. Blumenthal RD, Sharkey RM, Haywood L, et al. Targeted therapy of athymic mice bearing GW-39 human colonic cancer micrometastases with I-131-labeled monoclonal antibodies. *Cancer Res* 1992;52:6036–6044.
6. Siegel JA, Pawlyk DA, Lee RE, Sharkey RM, Horowitz J, Goldenberg DM. Tumor, red marrow, and organ dosimetry for ^{131}I-labeled anti-carcinoembryonic antigen monoclonal antibody. *Cancer Res* 1990;50:1039–1042.
7. Boerman OC, Sharkey RM, Blumenthal RD, Aninipot RL, Goldenberg DM. The presence of a concomitant bulky tumor can decrease the uptake and therapeutic efficacy of radiolabeled antibodies in small tumors. *Int J Cancer* 1992;51:470–475.

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REPLY: By its nature, mathematical modeling of biological processes lacks the self-assurance inherent in obtaining actual measured (rather than simulated) results. I am particularly grateful, therefore, to Drs. Sharkey, Blumenthal and Goldenberg (*1*) for pointing out that the conclusions arrived at in my recently published modeling analysis of radioimmunotherapy for micrometastases (*2*) concur with their own recent experimental observations (*3,4*). Their observation of diminished therapeutic efficacy with increasing size of the micrometastatic cell cluster is in qualitative agreement with model predictions. In particular, they have demonstrated 100% cure when targeting cell clusters at the very early stage of micrometastatic spread (*4*). Such work provides further experimental evidence that the optimum window of opportunity for targeting micrometastatic cells occurs when the cells are on the luminal side of the vascular basal lamina (i.e., directly accessible to circulating antibody). Since at any one time micrometastatic clusters within a patient will be at various stages of the metastatic cascade, multiple administrations of antibody, starting immediately after solid disease has been eliminated, will be required for success. Because of the complications associated with human anti-mouse activity (HAMA) that arises subsequent to the initial administration of mouse-derived antibody, such a protocol will be feasible only with genetically engineered human or humanized antibodies.

As noted by Drs. Sharkey, Blumenthal and Goldenberg, many issues and potential obstacles remain to be resolved. A key consideration in overcoming these obstacles is the highly case-spe-

cific nature of radioimmunotherapy. A set of parameters that are optimum under one set of conditions usually do not apply in general. The advantages of using antibody fragments to improve antibody targeting of solid tumors, for example, are not evident in targeting of micrometastatic disease since extravasation and diffusion of the antibody through the interstitial space are not required for targeting (*4*). One may anticipate that the currently popular radionuclide for radioimmunotherapy, ^{90}Y, will be inappropriate for targeting micrometastatic disease due to its long-range emissions. It is this case-specific nature of radioimmunotherapy that calls for the development of mathematical models and the application of computer simulations. By incorporating the salient features of a particular treatment protocol and accounting for the known biological parameters of a particular tumor and antibody-antigen combination, mathematical modeling analyses may help guide the experimental work and thereby reduce the scope of necessary human experimentation.

As the focus turns towards targeting of micrometastatic disease, mathematical modeling will become increasingly important in providing an assessment of potential therapeutic efficacy. Since it is not clinically feasible to determine the antibody concentration or the radioactivity associated with a microscopic cluster of metastatic cells, analytical techniques will be necessary to estimate antibody uptake and cell cluster absorbed dose, given the range of expected cluster sizes, their position relative to the vasculature (luminal versus interstitial) and blood pharmacokinetics.

Administering radiolabeled antibodies to patients that have no objective evidence of disease and without the ability to verify antibody targeting in vivo through external imaging may be unsettling to those accustomed to radioiodine therapy of thyroid disease or radioimmunotherapy of solid tumors. The potential for successful radioimmunotherapy in such a setting, along with the observation that chemotherapeutic trials have been undertaken with significantly less theoretical and experimental justification, should help overcome such reservations. Ultimate assessment of adjuvant or prophylactic radioimmunotherapy in the treatment of occult disease will require randomized trials with a 5-yr to 10-yr follow-up. Patience will therefore be required. The radioimmunotherapy community is well qualified in this regard.

REFERENCES

1. Sharkey RM, Blumenthal RD, Goldenberg DM. Radiolabeled antibodies as cancer therapeutics [Letter]. *J Nucl Med* 1993;34:1028.
2. Sgouros G. Plasmapheresis in radioimmunotherapy of micrometastases: a mathematical modeling and dosimetrical analysis. *J Nucl Med* 1992;33: 2167–2179.
3. Sharkey RM, Weadock KS, Natale A, et al. Successful radioimmunotherapy for lung metastases of human colonic cancer in nude mice. *J Natl Cancer Inst* 1991;83:627–632.
4. Blumenthal RD, Sharkey RM, Haywood L, et al. Targeted therapy of athymic mice bearing GW-39 human colonic cancer micrometastases with ^{131}I-labeled monoclonal antibodies. *Cancer Res* 1992;52:6036–6044.

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Diuretic Renography

TO THE EDITOR: The paper entitled "The Well Tempered Diuretic Renogram" (*1*), presented by the Society for Fetal Urology and the Pediatric Nuclear Medicine Council, appeared earlier in a more expanded form (*2*). In both presentations, one cannot quite distinguish whether the purpose is to explain the theoretical (physiopathological) basis for a procedure or to report on a technical methodology (e.g., region of interest (ROI) placement) which has been shown empirically to be superior to other methods. In the absence of either theoretical or empirical argumentation, on what exactly was consensus based?

For example, what is the physical meaning of a two-pixel wide background ROI? Even if we assume that the digital matrix will be in a 128 × 128 format, as recommended, two pixels would cover different sized regions, depending on detector size, zoom factor and the modulation transfer function of the imaging system.

It would have been useful to rationalize why separate sampling over the collecting system is necessary: if the collecting system is full, and if the compliance of the system has been exhausted, the obstruction must result in delayed cortical clearance, since fluid is not compressible. What interpretation is offered if cortical transit time and or diuretic response are normal, but are abnormal in the collecting system?

Third, to the extent that the kidney acts as a delay line, or even a mixing compartment, one should expect that clearance of the tracer from the kidney (or the output function) also reflects plasma clearance (or the input function) and not exclusively the transit function through the kidneys. This point has been made often and well (*3*), and its neglect in the discussion of interpretation is surprising.

Finally, the authors fail to describe what are or should be the criteria for success or failure of the test. Merely mentioning that there would be follow-up is hardly sufficient.

REFERENCES

1. The Society for Fetal Urology and The Pediatric Nuclear Medicine Council. The "well tempered" diuretic renogram: a standard method to examine the asymptomatic neonate with hydronephrosis or hydroureteronephrosis. *J Nucl Med* 1992;33:2047–2051.
2. Conway JJ. "Well tempered" diuresis renography: its historical development, physiological and technical pitfalls, and standardized technique protocol. *Semin Nucl Med* 1992;22:74–84.
3. Whitfield HN, Britton KE, Hendry WF, et al. Distinction between obstructive uropathy and nephropathy by radioisotope transit times. *Br J Urol* 1978;39:433–436.

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REPLY: Dr. Goris raises some interesting technical questions regarding our paper on "The Well Tempered Diuretic Renogram." His queries offer an opportunity to expand upon the reasons for and purpose of the Consortium report on the discussions which transpired during our initial meeting in 1989.

The Consortium of Nuclear Medicine Physicians was convened at the request of the Society for Fetal Urology (SFU). Members of the SFU had raised the concern that the diuretic renogram in the neonate as performed at their various institutions often did not correlate well with surgical findings. SFU members suggested that this might be related to variable methods of performing diuretic renography in their individual institutions.

The paper therefore is essentially a proceedings report from the meeting, which derived a consensus on the various methods of quantitatively measuring diuretic renogram response. The suggested methods should be utilized to gather data that eventually can be correlated with outcome and perhaps indicate which is the