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*).

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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-