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Importance of the Terminal Portion of Tumor Time-Activity Curve in Determining Tumor Dosimetry in Radioimmunotherapy

TO THE EDITOR The fine article by Eary et al. concerning the Seattle experience in treating lymphoma patients with the ^{131}I-labeled pan B-cell antibody MB-1 (*1*) was of considerable interest to us in view of our own ongoing experience with this same antibody (*2*). One aspect of this article which particularly intrigued us was the description of the methodology used to choose an appropriate antibody protein dose to achieve optimal tumor radiation doses relative to background. The general claim was made that higher protein doses resulted in more favorable tumor/normal organ dosimetry in patients without high tumor burdens. We have had the opportunity to study ^{131}I MB-1 biodistribution using 40-mg and 200-mg protein doses in three B-cell lymphoma patients with relatively low tumor burdens selected from a total of twelve patients in our series (*2*). Similar to the Seattle group's results, increasing the protein dose from 40 to 200 mg (given intravenously over 2 hr) resulted in slower blood clearance of radioantibody activity. We have also observed an increase in the predicted radiation doses delivered to tumors and normal organs with a higher protein dose per mCi administered. In our limited experience, however, we have not been able to demonstrate an increase in tumor radiation dose *relative* to normal tissues with the higher protein dose. Although our maximum protein dose was not as high as that used by Eary et al., our differing results from the Seattle experience prompted us to further examine the dosimetric methodology employed by the Seattle group.

Eary et al. state that their patients were imaged during the week following the injection of increasing antibody protein doses to calculate residence times in tumors and the normal organs, these residence times then being used for dosimetric determinations using the MIRD formalism. In examining their Figure 6 on page 1263 where these parameters are plotted for Patient 1 of the series, it is apparent that tumor/normal tissue radioantibody uptake ratios are substantially lower in the first 2 days following the higher antibody protein dose than at the lower protein dose. Only at later time points does the "dosimetric advantage" to tumor of the higher protein dose become apparent—due to what is plotted as an increased retention time in the tumors. In fact, the curve-fit provided suggests that the antibody-delivered radioactivity is completely retained in the tumors forever at the highest (1100 mg) protein dose, and this is so stated in the text.

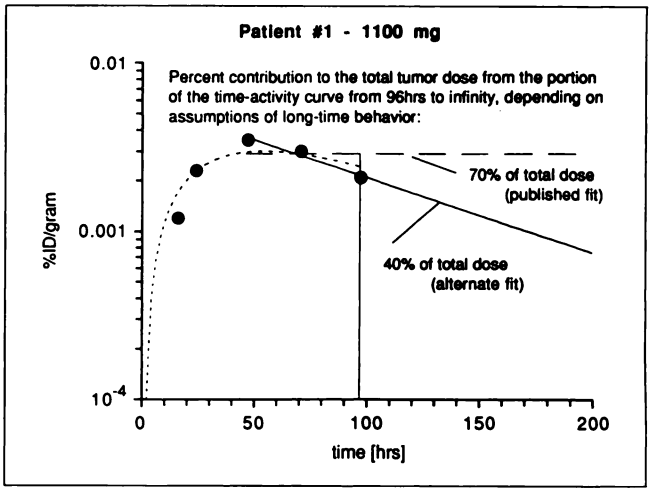

FIGURE 1. Tumor-activity curve indicates progressive decline in tumor activity.

While complete tumor retention of iodinated antibody may be the case in their other patients, in the example shown (Patient 1, Figure 6) at the 1100-mg dose, image data points are only presented through 96 hr postinjection, making fitting the terminal portion of the curve difficult. An alternate, and we believe more appropriate, fitting of the tumor-activity curve (our Fig. 1) indicates a progressive decline in tumor activity from 48 through 96 hr following injection, despite the authors' chosen graphical indication that the tumor does not lose any radiolabeled antibody. If the curve is fitted as "flat" beyond 96 hr, (i.e., no radiolabeled antibody clearance from the tumor), 70% of the total radiation dose to the tumor is from the curve tail (i.e., from beyond the last data point), while if the tumor activity from 24–96 hr and beyond is plotted as a downsloping exponential function, only 40% of the total tumor radiation dose is from the curve tail. With a flat tumor clearance curve, there is a 100% increase in predicted radiation dose to the tumor over that present if the declining clearance curve is used (i.e., 850 cGy versus 425 cGy). Thus, the quality of the data and the method chosen for fitting the terminal portion of the antibody activity curve are critical to the dosimetric estimate and to the conclusion that increased protein dose improves relative tumor dosimetry.

In summary, while we agree that higher antibody protein doses will prolong the circulation of the MB-1 radioactivity in the blood and accept that increased protein doses of MB-1 *may* increase absolute and relative tumor dosimetry/mCi, we believe that longer data acquisitions (beyond 4–5 days) and a multi-exponential fitting of tumor clearance data are essential for an accurate dose estimate. This is particularly true if the tail of the tumor radioactivity clearance curve is relatively flat (and thus contributing substantially to the radiation dose). In our experience, it is most unusual for antibody-delivered radioactivity, particularly ^{131}I activity, to be fully retained in any tumor site over time. If such radioactivity is retained in tumors with this degree of avidity, substantially delayed imaging points would be useful in confirming and better understanding the phenomenon.

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REPLY: It is indeed interesting to compare experience with the MB-1 antibody in lymphoma patients. Biodistribution data show that in antibody therapy administrations dosimetric advantage occurs at late times after infusion. This fact belies the importance of curve fitting techniques for time-activity data for normal organs and tumors. There are several methods to "fit" imaging data obtained at a few times to curves, all with positive and negative aspects to the assumptions they require. Probably the most important aspect of data interpretation is consistency in application of analytical techniques. This is particularly important in interpreting biodistribution data for dosimetry. The most critical aspect is a realistic error analysis on the various components of the dosimetry input data. For instance, what is the error in tissue quantitation using the gamma camera? The same questions could be asked of the count-based data from blood samples and tissue biopsies, as well as whole body counting techniques and dose calibrator measurements. In addition, there is error associated with curve fitting analysis and in the assumptions of MIRD program itself.

In our studies, the graphical best fit of time-activity curve data is interpreted in the context of other related biodistribution data gathered in the experimental infusion, all considered along with associated error. In addition to the data shown in the figure, we had late (usually 8 day) imaging times after the third patient infusion. These data confirmed that the tumors had a flat clearance curve. We are familiar with the various techniques for curve fitting and employ the method Wahl et al. suggest. Now, patients are routinely imaged at late times to reduce the error in curve fitting techniques, rather than asserting the correctness of one method over another. Image derived data is interpreted in the context of other biologic data gathered from the test infusion, most importantly serum clearance. Clearance half-times of the specific and nonspecific antibodies are similar (in patients receiving large antibody doses), suggesting antigen saturation and an antibody deposition rate that overcomes specific metabolism of the antibody. This evidence suggests that antibody-tumor residence time is prolonged without loss from the tumor at later times. Interpretation of biodistribution data for the purposes of estimating absorbed radiation dose requires integration of all data to make the most appropriate set of assumptions and to understand their associated error.

We are familiar with the experience of the Ann Arbor group using the MB-1 antibody in non-Hodgkin's lymphoma and would like to point out that their results are consistent with our findings. Infused doses of MB-1 antibody as low as 40-200 mg did not produce prolonged retention in tumors at late times. This was not achieved until doses of 10 mg/kg in the patient. Lower doses in patients with larger tumor burden were metabolized rapidly, and the serum clearance of specific antibody was not prolonged compared to the co-administered nonspecific antibody. Larger antibody doses in the Ann Arbor patient group would most likely yield the same results, and the comparison of the biodistribution data between the two groups would be interesting. We thank the authors for making these observations and look forward to a comparison of data from the two clinical trials.

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Myocardial Viability

TO THE EDITOR: Gropler and Bergmann (*1*) state that conclusions from my study (*2*) were based on whether tissue was "felt to be viable although functional assessments were not performed." The implication is that conclusions from this study were subjective (i.e., based on a feeling). In fact, viability was based on the well-validated histochemical stain, triphenyltetrazolium chloride (TTC) (*3–5*). Functional information, such as regional left ventricular wall motion, is a less sensitive measure of viability, as evidenced by improvement in contractility in tissue with FDG uptake following successful revascularization (*6*). By its strictest definition, viability indicates the presence of metabolically active tissue, not whether it is able to perform a specialized function. I would agree that the potential for improvement in regional function is a desirable property of any diagnostic test alleging to be a marker of viability. The data presented in the study of Gould et al. (*7*), showing concordance between FDG and rubidium-82 washout, suggest that revascularization would also show comparable changes in regional function.

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REPLY: It appears that Dr. Goldstein missed the point of our editorial (*1*). The biochemical processes that underlie myocyte life (i.e., the maintenance of ionic gradients and cellular homeostasis, normal electrophysiologic activity, and energy production and catabolism) are *prerequisites* for contractile function. Nu-