Nonuniform Distribution of Radiolabeled Monoclonal Antibody in Tumor

TO THE EDITOR: We found the article by J.L. Humm and L.M. Cobb very interesting (*1*). They describe how nonuniform distribution of radiolabeled antibody in tumor can influence the energy deposition at the cellular level. They also presented calculations of the mean energy deposition to individual cell nuclei derived from theoretical models.

In a recent study (*2*), we faced the same problem of heterogeneous intra-tumor antibody distribution at a macroscopic level. We studied tumors removed from patients after they had received i.v. doses of radiolabeled monoclonal antibody. Using quantitative autoradiography we were able to measure the local concentration of radiolabeled antibody in small regions within tumor.

The absolute distribution and amount of radioactivity (nCi/g) in tissue can be determined with quantitative autoradiography, but its resolution is 100 microns (*3*) so that calculations of radiation dose delivered to tumor are limited to that level of spatial resolution. On the other hand, microautoradiographic methods that show the distribution of antibody either on the plasma membrane or in the cytoplasm of individual cells are not useful for dosimetric calculations unless accompanied by a system of radioisotopic standards that define the absolute amount of radioactivity present.

In the Methods section the authors state that the gross heterogeneities in spatial distribution of antibody favor the choice of longer range beta-emitters and cite a previous work (*4*). We agree as this was the conclusion of our study. However, in considering the dosimetry at the cellular level, the authors found that there is a geometric enhancement of energy deposition in tumor cell nuclei due to membrane-bound antibody and that this enhancement is greatest for short-range emitting radionuclides, especially alpa-sources. It would be of interest to know whether the authors consider long-range or short-range radioactive emitters most efficacious for radioimmunotherapy.

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REPLY: Drs. Del Vecchio and Reynolds pose the question which at one time or another has exercised the minds of most people working in radioimmunotherapy (RIT), i.e., which is the most suitable radionuclide for therapy? But until we know a great deal more about the intra-tumor distribution of both targeting antibody (Ab) and the targeted stem cell, we will not be in a position to answer this question. So far our work has lead us to the opinion that no single radionuclide is likely to be suitable for all tumors.

Radiobiologic arguments point to the possible value of short range alpha-emitters, such as ^{211}At, where the radionuclide can be delivered to stem cells in an amount sufficient to result in >10 alpha-hits per cell (*1*). Because of difficulties in Ab access to tumors (*2*), this is more likely to occur with single or small groups of cells in the circulation or loosely aggregated tissues than for solid tumors.

When the delivery of radionuclides to the surface of an adequate number of stem cells is not possible, lethal radiation doses to the tumor stem cell population must be derived from the cross-fire resulting from the distant decays of longer-range emitting radionuclides, e.g., ^{90}Y or ^{131}I. However, a much larger quantity of Ab needs to be delivered to the tumor under these circumstances (*3*).

The remarks of Drs. Del Vecchio and Reynolds concerning the difficulties of performing quantitative autoradiography (ARG) and grain-source resolution are quite correct. For short-range sources, the relation to the source-to-grain location is critical and it is desirable to know the source coordinates to within 10 μm of accuracy. This requires the use of a source such as the Auger emitter, ^{125}I, in place of ^{131}I for the ARG. To relate the grain density on a section to the activity, i.e., to determine the efficiency of the autoradiographic process which depends on the radionuclide and section thickness, a series of standard ARGs containing known amounts of activity are required. We have found a quick method for the intercomparison of individual section activities, which works at activity levels following a therapeutic administration of radiolabeled Ab. This is to count each section directly at the face of a scintillation counter. One potential artifact which can occur during tissue fixation is the loss of activity to the fixative. The magnitude of activity loss can be determined by counting the fixative following specimen removal. Since the fixative will preferentially remove the free radionuclide or the unbound radioimmunoconjugate, the ARG may reflect a better bound/nonbound Ab distribution than is actually the case. Alternatively, sections can be counted prior to fixation.

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