EDITORIAL

Radioimmunotherapy of Micrometastases: Sidestepping the Solid-Tumor Hurdle

The potential of radiolabeled antibodies to treat micrometastases has long been recognized (*1–6*). In the treatment of solid disease, however, this recognition has not translated into clinical assessment. The emphasis has been instead on the treatment of bulky, measurable tumors. Although the rationale for this is relatively straightforward, the clinician must be able to measure tumor shrinkage to assess therapeutic effectiveness. Its apparent corollary, that the agent must demonstrate effectiveness in bulky disease before attempting treatment of disseminated disease, has hindered clinical assessment of radioimmunotherapy for micrometastases. This corollary is founded on principles that apply to chemotherapy and not necessarily to radioimmunotherapy.

As pointed out by DeVita et al. (*7*) the most important indicator of a chemotherapeutic agent's effectiveness is the complete response rate, which is the fraction of patients treated whose measurable (bulky) disease becomes undetectable. It has been hypothesized that treatment failure in chemotherapy is associated with the existence of one or more drug-resistant clones. Theoretical analysis of the time-course by which such clones develop was performed by Goldie and Coldman in 1979 (*8*), who used mathematical modeling to predict that tumor cells would mutate to drug resistance at population sizes between 1000 and 1 million cells. The clinically detectable level is 1 billion cells, which is 1000-fold greater and corresponds, approximately, to a 1-cm mass. Even at very low mutation rates, detectable masses would certainly have at least one drug-resistant clone. The absolute number of resistant cells in a tumor composed of 10^9 cells, however, could be relatively small. At the time of initial treatment, resistant clones could already be distributed and lead to distant metastases and/or they could remain localized and distribute following failure to control the primary tumor (*9–11*). This would predict that an effective chemotherapeutic agent should yield a partial or complete remission, which would then be followed by repopulation of resistant clones leading to a clinically detectable recurrence. Several conclusions emerged from that analysis:

1. Because resistant clones arise in undetectable tumor cell population sizes, resistance should be a problem even with small tumor burdens or micrometastases.
2. Because a particular clone may be resistant to one agent but not another, a cure is most likely if all available effective drugs are delivered simultaneously (*7*).

In short, there is no reason to expect effectiveness against minimal disease following radiotherapy or surgery if an agent or combined agents have not demonstrated effectiveness with measurable disease. This conclusion suggests that the traditional rationale for anticipating greater effectiveness when targeting minimal disease, i.e., there are less cells to kill so that it should be easier to kill all of them, is not compelling enough to bypass the initial, bulky-tumor assessment of a new chemotherapeutic agent.

In radioimmunotherapy, failure has not been associated with the existence of a resistant clone but, rather, with inadequate delivery. A preponderance of evidence indicates that large 150,000 molecular weight proteins do not readily distribute throughout a solid tumor mass, despite the increased transcapillary movement that is associated with tumor vasculature (*12–29*). This evidence, along with several studies predicting improved effectiveness in targeting micrometastases (*30–41*) provides an additional rationale for an anticipated improvement in effectiveness when targeting micrometastases, i.e., improved delivery.

The chemotherapeutic rationale for requiring efficacy against measurable disease before assessing an agent's efficacy in an adjuvant setting is not applicable to radioimmunotherapy because (a) failure in radioimmunotherapy is associated with inadequate delivery rather than the existence of resistant clones and (b) the advantage of targeting minimal disease with radioimmunotherapy is not limited to the increase in cure probability associated with killing a smaller number of cells. It also includes the significant improvements in delivery that are associated with smaller tumor cell cluster dimensions.

When we finally overcome the chemotherapeutic paradigm and start examining the efficacy of radioimmunotherapy in an adjuvant setting, a cautious and studied approach must be taken. Variability in tumor-cell antigen expression, the analog to clonal resistance, may emerge as a significant problem (*42*); extravascular (i.e., sanctuary) sites of even minimal disease may continue to pose a delivery problem; failure may also arise from difficulties that have no analog in chemo- or radiotherapy.

The work of O'Donoghue et al. examines one such difficulty (*43*). They demonstrated that tumor control probability associated with different beta-emitting radionuclides achieves a

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maximum at a tumor cell number greater than one. In other words, the single tumor cell presents a greater therapeutic challenge than a cluster of cells. As demonstrated in their article, the optimal dimensions of a tumor cell cluster depend on the radionuclide. The optimal range of dimensions for most of the radionuclides listed are below clinical detectability. If the kinetics of antibody penetration are also considered, the optimal ranges are very likely to fall significantly below clinical detectability for all of the radionuclides (*12,30–32*). Does this mean that radioimmunotherapy will only work against micrometastases? No. It does, however, mean that it should be most effective in an adjuvant setting. Clinical trials designed to assess effectiveness in an adjuvant setting must be very carefully designed and performed because it may not be possible to assess efficacy on a case-by-case basis as is possible by measuring bulky tumor shrinkage.

In their analysis of the clinical implications of their work, O'Donoghue et al., provide an excellent example of how theoretical results may be used to improve the design of clinical trials. Unless it becomes possible to characterize the number and size distribution of micrometastases in individual patients at different times in the course of their disease (*11,44*), a combination of radionuclides intended to cover as large a range of tumor cell cluster dimensions as possible is necessary. Unless radionuclides that are efficient at eradicating single cells are used in radioimmunotherapy (*33,45–49*), adjuvant radioimmunotherapy will result in cures only if combined with another treatment modality. In a similar manner, it may be necessary to combine antibodies against different antigens to overcome the potential difficulties of variable or inadequate antigen expression.

To begin examining these issues, we must sidestep the solid tumor hurdle. Does this mean that the therapeutic response of bulky tumor to a radiolabeled antibody is not relevant to the further pursuit of that particular radiolabeled antibody for targeting micrometastases? Yes. Those qualities that make a radiolabeled-antibody combination ideal for targeting solid disease generally make it worse for targeting micrometastatic disease. Yttrium-90 has been proposed for targeting solid disease in part because the range of its emissions may help overcome the nonuniform distribution of antibody in larger tumors. As shown by O'Donoghue et al., this radionuclide is among the least effective for clinically undetectable micrometastatic disease. Antibody forms that penetrate more rapidly throughout a solid tumor generally do so at the expense of affinity. In targeting smaller, more penetrable clusters, such agents are only left with the disadvantage of reduced affinity.

Clinical evidence now exists in the treatment of hematologic disease that demonstrates the potential value of radioimmunotherapy in an adjuvant setting (*50*). In solid tumor disease, the inability to monitor shrinkage in assessing effectiveness against micrometastases may seem to be a severe limitation. This limitation will diminish over time as surrogate markers are developed (*51*). It is also important to note that much more detailed pharmacokinetic information may be obtained with radiolabeled antibodies via external imaging than is available in most assessments of new chemotherapeutic agents. In this regard toxicity is much more predictable and, as expected, has been largely limited to the hematopoietic system.

The article by O'Donoghue et al. (*43*) illustrates one of the fundamental differences between radioimmunotherapy and chemo- or radiotherapy. An acknowledgment of such differences and a reassessment of the paradigm that is being used to evaluate the potential effectiveness of radioimmunotherapy under different settings is needed so that we may begin clinical trial examination of adjuvant radioimmunotherapy for solid disease.

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