

Penetrating the Barriers to Successful α -Radioimmunotherapy

Sean Carlin, PhD

Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania

*For "up an' down an' round," said 'e, "goes all appointed things,
An' losses on the roundabouts means profits on the swings!"*

—Patrick R. Chalmers, "Roundabouts and Swings," 1914

There have been many significant advances in the field of radioimmunotherapy since the initial clinical studies were conducted in the 1980s. The emergence of monoclonal antibody technology, high-specific-activity labeling chemistries, and molecular engineering techniques have addressed several of the initial limitations encountered (1), resulting in the first Food and Drug Administration approvals of radioimmunotherapy with β -particle-emitting isotopes (β -radioimmunotherapy) for lymphoma.

The utility of β -radioimmunotherapy, however, is restricted largely to hematologic malignancy, with limited success reported in solid tumors. A central issue for conventional systemic β -radioimmunotherapy of bulky solid tumors is the therapeutic index, in that there is now a sufficient body of evidence to conclude that, irrespective of radionuclide used or antigen targeted, antitumor efficacy is observed only at doses that result in significant toxicity, principally to bone marrow and liver. This inadequacy results from some inherent features of β -radioimmunotherapy: in addition to poor antibody penetration, the slow blood clearance of antibody, combined with the millimeter-to-centimeter range of the energetic emission from radioactive decay, culminates in increased background absorbed doses and consequently reduced tumor-to-background ratio. A second limiting factor in this setting is that the antitumor efficacy of a given β -radioimmunotherapy dose decreases with tumor size, because of the proportional increase in the correctly targeted radiation dose that is deposited outside the tumor volume and therefore wasted (2). Essentially, long-range β -radioimmunotherapy becomes less effective as solid tumors get smaller. Despite these shortcomings, the potential to specifically target occult metastatic lesions on the basis of tumor antigen expression makes alternative radioimmunotherapy strategies worthy of exploration. The use of pretargeting strategies designed primarily to reduce normal-tissue dose are seeing renewed interest because of the emergence of a new generation of chemical components (3,4).

An article by Palm et al. (5) in the April issue of *The Journal of Nuclear Medicine* focused on the implementation of radioimmunotherapy with α -particle-emitting radionuclides (α -radioimmunotherapy). The rationale for the use of α -radioimmunotherapy is based principally on the greater cytotoxicity and shorter range of the α -particle than of the β -particle, resulting in increased antitumor efficacy combined with decreased normal-tissue toxicity. This rationale was recently demonstrated with the success of ^{223}Ra -dichloride (Xofigo; Bayer) for prostate cancer metastatic to bone (6), versus the minimal survival benefit reported previously from a range of similarly targeted β -isotopes (^{32}P , ^{89}Sr , ^{153}Sm) (7). Recent reports of dramatic prostate cancer responses to ^{213}Bi - and ^{225}Ac -prostate-specific-membrane antigen small-molecule compounds (8,9) also lend support to the case for targeted α -particle therapy, but as yet no information on renal toxicity (likely to be dose-limiting) in these cases is available.

α -radioimmunotherapy is optimally suited to single-cell, micro-metastatic, and minimal residual disease because of 2 governing factors: the poor tumor penetration of intact IgG and the short α -particle range (~ 80 – $100\ \mu\text{m}$). For lesions of these dimensions ($< 100\ \mu\text{m}$ in diameter), antibody binding to only the outer cell layers still places all malignant cells within the α -particle range. However, in bulkier disease conformations, the poor penetration of IgG into the tumor mass results in heterogeneous antibody (and radiation dose) distribution and consequent underdosing of non-targeted tumor cells. Tumor penetration of IgG is influenced by a combination of factors, including tight gap junctions (elegantly demonstrated by Sutherland et al. using autoradiography of avascular multicellular spheroids (10)), the physical barrier presented by tumor desmoplastic stroma, and the "binding-site barrier" first proposed by Fujimori et al. (11), a term that describes the phenomenon of reduced tumor diffusion of high-affinity antibodies resulting from the low antibody-antigen dissociation rate. This low rate, combined with abundant local target antigen, results in persistent antibody localization in the region of antibody delivery (usually perivascular) and inhibition of antibody dissemination throughout the tumor. The consequences of nonuniform antibody (and thus radiation dose) distribution, thoroughly examined by O'Donoghue (12), are common for all targeted radionuclides and have increasingly important ramifications as the tumor volume increases relative to the particle range. Put simply, short-range α -radioimmunotherapy becomes less effective as solid tumors get larger.

From this fact, it is easy to conclude that there can be no best single antibody-radioisotope pairing for the treatment of both large ($> 1\ \text{mm}$ in radius) and small ($< 50\ \mu\text{m}$ in radius) tumor deposits and that the selection of either α - or β -emitting isotopes will result in increased efficacy in one disease conformation at the

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For correspondence or reprints contact: Sean Carlin, Department of Radiology, University of Pennsylvania, 3620 Hamilton Walk, Philadelphia, PA 19129.

E-mail: carlins@mail.med.upenn.edu

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expense of the other. Gains on the swings mean losses on the roundabouts.

In the study by Palm et al. (5), a combined kinetic and dosimetric model is used to identify methods that maximize α -particle therapy for a larger tumor size range, based on short-range α -radioimmunotherapy with ^{211}At -MX35 (5). The model itself contains many parameters derived from the previous extensive clinical study of the intraperitoneal administration of ^{211}At -labeled MX35 and fragments thereof, recognizing a cell-surface antigen expressed on 90% of human ovarian epithelial cancers (13,14). ^{211}At is an α -emitting radiohalide with a half-life of 7.2 h, 100% α -particle yield per decay, and no significantly problematic daughter isotopes.

The model presented recapitulates in detail many of the issues outlined above— α -particle sterilization of tumors with radii larger than about 50 μm relies on antibody diffusion to the subsurface layers, and the inherent poor penetration of IgG over the short half-life of ^{211}At results in heterogeneous distribution and subsequent underdosing to central subregions of these larger deposits.

One seemingly straightforward means to overcome the binding-site-barrier issue for α -radioimmunotherapy in larger tumors is via the mass effect. This involves preloading with a large dose of unlabeled antibody to saturate the easily available tumor binding sites and thus facilitate improved tumor penetration of the α -radioimmunotherapy. This approach has proven effective, and is routinely used, for some β -radioimmunotherapy strategies (15–17). However, the study by Palm et al. (5) revealed that overcoming the tumor penetration issue in this manner also reduces absorbed doses in correctly targeted microtumors (<50 μm in radius) to subtherapeutic levels, because of lowered absolute α -radioimmunotherapy uptake. Again, swings and roundabouts—improved penetration in larger lesions comes at the cost of lower total absorbed dose in the smaller ones.

The major outcome of this study was the finding that, rather than adopting a preloading strategy, the administration of α -radioimmunotherapy at high specific activity, followed several hours later by a subsequent, much larger, administration of cold antibody (posttreatment dose), results in curative absorbed doses to all tumors up to 300 μm in radius. The model predicts that, in the larger tumors, administration of this posttreatment dose of cold antibody saturates the easily accessible surface antigen population, improving the redistribution and penetration of the α -radioimmunotherapy and essentially moving the binding-site barrier inward from the surface. Microtumors smaller than 50 μm in radius remain susceptible to this treatment, as their readily available binding sites are saturated by the α -radioimmunotherapy before the postloading, and the time between α -radioimmunotherapy and posttreatment administration allows for sufficient accumulation of sterilizing α -decays. The posttreatment cold antibody modification therefore potentially increases the overall antitumor efficacy of a given dose of α -radioimmunotherapy, specifically targeting a disease conformation (50–300 μm in radius) previously resistant to both α - and β -radioimmunotherapy without additional toxicity to bone marrow.

This beneficial effect exploits the similarity between the half-life of the isotope (^{211}At , 7.2 h) and the temporal dynamics of antigen saturation, governed by the binding affinity rate constants (the on-rate and the off-rate). In the models used, antibody saturation of peripheral binding sites was maximal between 2.5 and 7.5 h after administration of α -radioimmunotherapy. Given these parameters, this postloading strategy is

therefore unlikely to have a major effect on the efficacy of α -radioimmunotherapy using isotopes with longer half-lives (^{225}Ac , 10 d), and the applicability of this strategy to the α -isotopes with very short half-lives (e.g., ^{213}Bi , 45 min) remains to be fully examined. It is also important to keep in mind that the kinetic parameters relating to antibody concentration and initial antigen saturation rates used are likely to be specific to an intraperitoneal administration and do not necessarily apply directly to the systemic administration of antibody.

There is an ongoing debate surrounding the optimal use of radioimmunotherapy as part of a multimodal treatment strategy. Although the concept of radioisotope cocktails was proposed over 2 decades ago (2), and more recently was investigated in preclinical and limited clinical settings (18,19), there are still many conceptual and regulatory roadblocks to the implementation of such a strategy. Novel targeted radiotherapies are held to a much higher standard of individual-organ dose quantification than are equivalent targeted chemotherapies, for which establishment of an empirically derived maximum tolerated dose is generally sufficient. Accurate α -particle dosimetry is inherently complex, and it is not clear that the currently accepted organ dose tolerances, originally laid down by Emami et al. in 1991 (20), have any direct relevance to tissue response after α - (as opposed to β - or photon) irradiation.

As a result of these potential hurdles, whether actual or anticipated, the theory that some combination of α - and β -radioimmunotherapy would produce an optimal response in patients with a spectrum of tumor sizes remains largely untested and certainty warrants a more detailed investigation as the availability of novel α -radioimmunotherapies increases over the coming years. The findings in the study by Palm et al. (5) raise the intriguing possibility that the sequence of α -radioimmunotherapy followed by cold antibody and subsequent β -radioimmunotherapy may provide a route to incorporating all these elements to their maximal efficacy. Apropos to the swings and roundabouts, it would appear that the maximum recipient benefit and provider profit might be obtained by optimally combining the use of both inventions.

In conclusion, whereas the use of short-half-life radioisotopes directly conjugated to intact antibodies with long circulation times has previously been considered incongruent, the study by Palm et al. (5) suggests that a timed manipulation of the α -radioimmunotherapy-specific activity in vivo may present a way to maximize the effectiveness of this approach in treatment-resistant microtumors with minimal additional toxicity. Despite this advance, α -radioimmunotherapy remains unlikely to prove an effective monotherapy for large solid tumors, and establishing the precise role of α -radioimmunotherapy in a multimodal treatment plan needs to be prioritized. Accurate measures of absorbed dose in tumor and normal tissue, and the specific biologic consequences of this dose in each, are needed to better define this role. As is aptly demonstrated in this study, the use of increasingly sophisticated mathematic modeling can provide one means to design proof-of-concept studies and derive the preclinical data required to move the field forward.

DISCLOSURE

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