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Penetrating the barriers to successful alpha-radioimmunotherapy

Sean Carlin, PhD

Department of Radiology

University of Pennsylvania

Philadelphia, PA, 19104

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 b1872

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

The utility of β-RIT, however, is limited largely to hematologic malignancy, with limited success reported in solid tumors. A central issue for conventional systemic β-RIT of bulky solid tumors is that of therapeutic index – 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 which result in significant toxicity, principally to bone marrow and liver. This inadequacy results from some inherent features of β-RIT: in addition to poor antibody penetration, the slow blood clearance of antibody, combined with the millimeter/centimeter range of the energetic emission from radioactive decay, culminates in 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-RIT dose decreases with tumor size, due to the proportional increase of the correctly-targeted radiation dose that is deposited outside the tumor volume and therefore wasted(*2*). Essentially, long-range β-RIT becomes less effective as solid tumors get smaller. Despite these shortcomings, the potential to specifically target occult metastatic lesions based on tumor antigen expression makes alternative RIT strategies worthy of exploration. The use of pre-targeting strategies designed primarily to reduce normal tissue dose, are seeing renewed interest due to the emergence of a new generation of chemical components(*3,4*).

The article in this issue of the JNM by Stig Palm and colleagues(*5*) focuses on the implementation of RIT with alpha-particle-emitting radionuclides (α-RIT). The rationale for the use of α-RIT is based principally upon the greater cytotoxicity and shorter range of the α-particle, resulting in increased anti-tumor efficacy combined with lower normal tissue toxicity. The alpha rationale has recently been demonstrated with the

success of 223-radium dichloride (Xofigo) 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-PSMA small molecule compounds(*8,9*) also lends support to the case for targeted alpha-particle therapy, but as yet no information regarding renal toxicity (likely to be dose-limiting) in these cases is currently available.

α-RIT is optimally suited to single cell, micrometastatic and minimal residual disease due to two governing factors – the poor tumor penetration of intact IgG, and the short alpha particle range (~80-100 μm). For lesions of these dimensions (< 100μm diameter), antibody binding to only the outer cell layers still places all malignant cells within the alpha-particle range. However, in bulkier disease conformations, the poor penetration of IgG into the tumor mass results in heterogenous antibody (and radiation dose) distribution, and the consequent under-dosing of non-targeted tumor cells. Tumor penetration of IgG is influenced by a combination of factors, including due to 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 (*11*). This term describes the phenomenon of reduced tumor diffusion of high-affinity antibodies resulting from the low antibody-antigen dissociation (Koff) 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 non-uniform 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-RIT becomes less effective as solid tumors get larger.

From this, it is easy to conclude that that there can be no 'best' single antibody-radioisotope pairing for the treatment of both large (<~ 1mm radius) and small (>50 μm radius) tumor deposits, and that the selection of either alpha or beta-emitting isotopes will result in increased efficacy in one disease conformation at the expense of the other. Gains on the swings mean losses on the roundabouts.

In the study by Stig Palm and colleagues, use of a combined kinetic and dosimetric model is made to identify methods that maximize alpha-particle therapy for a larger tumor size range, based upon the short-range α-RIT ^{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*). At-211 is an alpha-emitting radiohalide with a half-life of 7.2 hours, 100% alpha-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 ~50 μm relies on antibody diffusion to the sub-surface layers, and the inherent poor penetration of IgG over the short half-life of 211At results in heterogeneous distribution and subsequent under-dosing to central sub-regions of these larger deposits.

One seemingly straightforward means to overcome the binding site barrier issue for α-RIT in larger tumors is via the mass effect. This involves pre-loading with a large dose of unlabeled antibody, result in saturation of the easily-available tumor binding sites, and thus facilitating improved tumor penetration of the α-RIT. This approach has proven effective, and is routinely employed, for some β-RIT strategies (*15-17*). However, the current study reveals that overcoming the tumor penetration issue in this manner also

results in reduction of absorbed doses in correctly-targeted microtumors (<50um radius) to sub-therapeutic levels, due to lowered absolute α-RIT 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 is the finding that, rather than adopting a pre-loading strategy, the administration of α-RIT at high specific activity, followed several hours later by a subsequent, much larger administration of cold antibody (post-treatment dose), results in the curative absorbed doses to all tumor sizes up to 300 μm in radius. The model predicts that, in the larger tumors, administration of this post-treatment dose of cold antibody saturates the easily-accessible surface antigen population, improving the redistribution and penetration of the α-RIT, essentially moving the binding site barrier inwards from the surface. Microtumors less than <50μm radius remain susceptible to this treatment, as their readily-available binding sites are saturated by the α-RIT prior to the post-loading, and the time between α-RIT and post-treatment administration allows for sufficient accumulation of sterilizing alpha decays. The post-treatment cold antibody modification therefore potentially increases the overall anti-tumor efficacy of a given dose of α-RIT, specifically targeting a disease conformation (50-300 μm radius), previously resistant to both α- and β-RIT without additional toxicity to bone marrow.

It should be noted that this beneficial effect exploits the similarity between the half-life of the isotope (At-211, $t_{1/2}$ 7.2 hours) and the temporal dynamics of antigen saturation, governed by the binding affinity rate constants (K_{on} and K_{off}). In the models used, antibody saturation of peripheral binding sites was maximal between 2.5 and 7.5 hours post-administration of α-RIT. Given these parameters, this post-loading strategy is therefore unlikely to have a major effect on the treatment efficacy of α-RIT utilizing isotopes with longer half-lives (Ac-225, $t_{1/2}$ 10 days), and the applicability of this strategy to the very short half-life alpha-isotopes (e.g. Bi-213, $t_{1/2}$ 45 minutes) 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 utilization of RIT as part of a multimodal treatment strategy. Whilst the concept of radioisotope 'cocktails' was proposed over two decades ago(*2*), and more recently 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 much higher standard of individual organ dose quantification than equivalent targeted chemotherapies, where establishment of an empirically-derived maximum tolerated dose is generally sufficient. Accurate alpha-particle dosimetry is inherently complex, and it is not clear that the currently-accepted organ dose tolerances, originally laid down by Emami in 1991(*20*) have any direct relevance to tissue response following alpha (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-RIT 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-RITs increases over the coming years. The findings in the study by Palm et al raise the intriguing possibility that the sequence of α-RIT followed by cold antibody and subsequently β-RIT may provide a route to incorporating all of these elements to their maximal efficacy. Apropos to the swings and roundabouts, it would appear that the maximum recipient benefit and provider profit might obtained by optimally combining the use of both inventions.

In conclusion, whilst the use of short half-life radioisotopes directly conjugated to intact antibodies with long circulation times has previously been considered incongruent, the study in this issue by Palm *et al* suggests that a timed manipulation of the α-RIT 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-RIT remains unlikely to prove an effective monotherapy for large solid tumors, and establishing precise role of α-RIT 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 mathematical modeling can provide one means to design proof-of-concept studies and derive the pre-clinical data required to move the field forward.

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