Cancer Research

α-Particle–Emitter Radiopharmaceutical Therapy: Resistance Is Futile

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Alpha-emitter radiopharmaceutical therapy (α-RPT) is a treatment modality that is impervious to conventional cellular resistance mechanisms because of the unique properties of the α-particle. Radiobiological studies of α-particle emitters have been few as they require detailed consideration of both biology and physics. Clinical studies of this radiation delivery modality have shown highly promising results in cancers that are resistant to other treatments. The work by Yard and colleagues published in this issue introduces an innovative approach to radiobiological investigations of α-RPT and highlights the specific physics considerations required to properly investigate this multidisciplinary treatment modality.

See related article by Yard et al., p. 5640

Alpha-particle emitter radiopharmaceutical therapy (α-RPT) is an emerging and promising cancer treatment strategy that is fundamentally different from all other cancer therapies. α-Particles are helium nuclei emitted from radioactive atoms, also known as radionuclides. Depending on the energy with which they are emitted from the radionuclide, they travel 50–90 μm in the tissue. They are highly potent because they deposit energy along their track at an ionization density that is 100–1,000 times greater than that of radiotherapy or radiopharmaceutical therapy with β-particle emitters; this is dependent on where along the track the deposition event happens. The DNA damage caused by such highly ionizing tracks is predominantly double-stranded and often massively disruptive. Accordingly, a small number of α-particle traversals through the cell nucleus can cause cell death (1). α-Particles are typically delivered to cancer cells by conjugating α-particle–emitting radionuclides to agents that concentrate on, or are in the immediate vicinity of, tumor cells. Treatment is not delivered by an external beam but rather systemically or by locoregional injection. Comparison of α-emitter therapy to other systemic therapies in preclinical cancer models has shown that α-emitters are far more effective than currently available agents (2, 3). Importantly, clinical studies have shown benefit to patients with cancers considered refractory to all available treatment modalities (4–6).

Investigations into the radiobiology of α-particles date back to the early 1960s. One of the first studies investigating cell sensitivity to α-particles was conducted by Barendsen (7). Using a kidney cell line, he elucidated the relationship between α-particle energy and cellular radiosensitivity. He found that for the same absorbed dose, kidney cells were up to 8 times more sensitive to α-particles than to photon radiation, giving α-particles a relative biological effectiveness (RBE) as high as 8. In addition, it was observed that 110 keV of α-particle energy was deposited in tissue per micron traveled by the α-particle; for comparison, the corresponding linear energy transfer for electrons, photons, or gammas rays is 0.2–0.5 keV/μm.

In this issue of *Cancer Research*, Yard and colleagues used 28 cancer cell lines to examine the relationship between gene expression patterns, sensitivity to α-particle therapy, and RBE (8). They introduced a high throughput approach for evaluating RBE. The traditional approach requires that a dose versus response relationship be established for a "reference" radiation such as sparsely ionizing radiation and the "test" radiation, which, in this case, is α-particles. The RBE would be the ratio of the reference radiation absorbed dose to the α-particle absorbed dose required to achieve a particular response. In cell culture studies, the response is measured as the fraction of cells that retain the ability to form clonogens (i.e., the cellular surviving fraction). Measuring this requires plating an appropriate number of cells initially, so that after radiation exposure an adequate number of colonies are formed to obtain a reliable measurement of the surviving fraction. Colonies are usually counted 2–3 weeks after irradiation. These steps are laborious, time-consuming, and not amenable to high throughput evaluation of α-emitter RPT. Instead Yard and colleagues developed a proliferation assay that requires 9–11 days. They showed good correlation between their high throughput assay and the colony formation assay.

The assay was used to compare the sensitivity of each of the 28 cell lines to sparsely ionizing radiation delivered by an external beam with that delivered by α-particles emitted by radium-223 and its four α-particle–emitting daughters. This comparison highlights a unique and physics-heavy aspect of RPT-related studies. Both the external beam of photons and radium-223 deliver radiation. The amount delivered by the external beam is always expressed as an absorbed dose, defined as the ionizing energy absorbed by a mass of tissue or cells divided by the mass of tissue that is absorbing the energy, essentially the energy density. The unit for this quantity is the gray (Gy). Because external beams deposit their energy onto a well-defined field from an external source of radiation, a measurement at the position where the cells will be placed provides the absorbed dose that will be delivered to

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the cells per unit time when the beam is turned on. While the measurable quantity of the external beam is the absorbed dose, for RPT the measurable quantity is the radioactivity administered to a patient or the radioactivity concentration in a petri dish. Radioactivity, or more rigorously, activity, is the number of disintegrations per second. The corresponding unit is the becquerel (Bq). In RPT, absorbed dose is a calculated quantity. The calculation must account for the spatial distribution of the parent and daughter α-emitting radionuclides, the range of the emissions, and the geometry of the target volume for which the absorbed dose is desired. For example, with α-RPT the absorbed dose to the cytoplasm can be different from that to the nucleus. Both, the values and the degree to which they differ will depend on their geometry and the spatial distribution of the emissions. In external photon beam radiotherapy, these considerations are not a concern because the dose is delivered uniformly regardless of cell dimensions or configuration. To compare the biologic effects of α-RPT relative to sparsely ionizing radiation/external beam, Yard and colleagues had to consider all these effects. They assumed that the Ra-223 and its daughters are uniformly distributed in the incubating media outside the cell. Given such a spatial distribution at the cellular level, they should then account for the α-particle path length through the nucleus and through the cytoplasm. Because the energy deposition rate of an α-particle depends on its kinetic energy or distance from the emission source, the specifics of where the particle originated, the direction in which it traveled, and where it stopped are all important in calculating the absorbed dose. Fortunately, as cited by Yard and colleagues, the process for doing all of this has been previously established. Yard and colleagues used this to calculate the absorbed dose to cell nuclei. In evaluating the potential biologic response of radiopharmaceutical therapy, a calculation of the absorbed dose to the relevant target volume is essential. This was illustrated when the authors noted that the addition of hydroxyapatite (HA) resulted in a significant reduction in survival for the same activity concentration. By performing a dose calculation that accounted for the change in geometry due to the addition of HA, they showed that the apparent increase in cell line sensitivity was really a result of a greater absorbed dose delivered to the cells rather than some intrinsic biological increase in sensitivity associated with the presence of HA. Of course, this does not negate the observation that the addition of HA increased cell death, in fact, it illustrates the complex intermixture of physics and biology that characterizes RPT and in particular α-emitter RPT.

By comparing the photon versus α-particle radiosensitivity of cells with mutations in one of the pathways that regulate the oxidative stress response, the investigators confirmed the one constant in all biological studies of α-particle efficacy versus other modes of cell kill—α-particles are much more potent and largely impervious to resistance. Consistent with this, the authors were careful not to characterize any of the cell lines as resistant, rather the terminology used is reduced sensitivity. Some biological insight regarding the variability in tumor cell sensitivity to α-particles across the 28 tumor cell lines was obtained by analyzing the gene expression of the cell lines and also to some extent by the observation that cells with larger cytoplasmic radii exhibited greater α-particle radiosensitivity. The genomic screen found that PIK3CA-activating mutations were strongly associated with decreased sensitivity to α-particles. To confirm that PIK3CA mutations decrease sensitivity to α-particles, they generated cell lines containing the most frequently mutated protein-coding domains. The sensitivity analysis demonstrated decreased sensitivity of the PIK3CA-mutated cell lines relative to the wild-type. The reduction in sensitivity was approximately 20%–25% of the null and wild-type cell lines, well within the range of sensitivities found across the 28 cell lines. The authors wisely included both the high-throughput proliferation marker–based assay and the rigorous colony formation assay to clearly demonstrate the difference in radiosensitivities between the different cell lines. While the proliferation marker–based assay is a valuable and convenient tool for high-throughput analysis, one must go back to the basics for the definitive evaluation of radiosensitivity.

Returning to the physics biology intertwine, the authors allow for the possibility that the significant relationship between α-particle sensitivity and the nuclear to cytoplasmic radius may result from internalization of some small fraction of the extracellular radium due to its binding to ferritin receptors. This would change the distribution of Ra-223, the absorbed dose calculation, and therefore the apparent radiosensitivity. The focus of this article was on identifying markers of resistance; the alternative, identifying markers of susceptibility, has also been demonstrated by examining the fidelity of cellular DNA double-strand break repair pathways (9, 10).

The results presented by Yard and colleagues are consistent with the notion that α-particle cell lethality is impervious to eukaryotic cell resistance mechanisms and, extrapolating from this, that treatment failure in a clinical context is much more likely to arise by a failure to deliver α-particles to the relevant cell targets than to biological resistance mechanisms. α-RPT and radiopharmaceutical therapy, in general, is a multidisciplinary endeavor. Logistical, isotope supply, and clinical practice challenges remain before α-RPT is widespread and routine. Fortunately, steady progress is being made in each of these areas.

Disclosure of Potential Conflicts of Interest

G. Sgouros is a consultant (paid consultant) at Bayer, Inc, and scientific advisory board member at Areva Med. No other potential conflicts of interest were disclosed.

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