

EDITORIAL



Fighting Prostate Cancer with Radium-223 — Not Your Madame's Isotope

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As each year ushers in new and innovative survival-enhancing treatments for castration-resistant prostate cancer with bone metastases, patients and their physicians have a sense of empowerment associated with this growing therapeutic arsenal.¹⁻⁵ Nonetheless, nearly 30,000 men still die from prostate cancer every year, and many have debilitating illness from osseous involvement. For this latter group, Alpharadin in Symptomatic Prostate Cancer Patients, a randomized, placebo-controlled study reported by Parker et al. in this issue of the *Journal*, focuses on a new weapon in anticancer therapy.⁶

Radium-223 dichloride (radium-223), the first alpha emitter to undergo phase 3 testing and receive approval for clinical use, acts independently of cell cycles, surface markers, and tumor types. The simplicity of the alpha emitter radium-223 lies in its winning combination of a convenient half-life (11.4 days) and its inherent bone-seeking and potent DNA-damaging properties. The authors describe a well-executed international, multicenter trial showing an overall survival benefit associated with radium-223 in more than 900 patients with prostate cancer. The real-world applicability is undeniable; these patients had symptomatic skeletal disease and had received previous or concurrent complementary therapies.

No discussion of radium is complete without first acknowledging Madame Marie Curie, who with her husband Pierre first isolated radium-226 from pitchblende. Despite the current widespread availability of radiopharmaceutical agents, short-lived alpha emitters that are suitable for intravenous medical therapy have been limited until recent advances in radiochemical separation and

cyclotron-based production of alpha emitters made their generation feasible. Yet, obstacles to their use may still exist. Alpha particles traditionally provoked fear in the lay public and nervousness in the medical community (including some radiation safety officers) because of their enhanced relative biologic effectiveness. The concept of relative biologic effectiveness combines physical linear energy transfers with the radiobiologic effects of ionizing radiation in tissue to provide a medically relevant scale for comparing the potencies of various forms of ionizing radiation. The relative biologic effectiveness of alpha emitters, which is several times that of traditional x-rays (depending on the tissue type), is their most and least attractive feature. Alpha particles are efficient, and they cause cell damage with a single knockout as compared with gamma rays and beta particles. Such killing power is rendered unattractive if it is coupled with an unforgiving half-life.

Historically, safety concerns stemmed from the 1601-year half-life of radium-226 and its decay into volatile radon gas. These concerns were further fueled by horror stories that included lost radium sources that underwent accidental heat sterilization and vaporization and closed down entire hospitals.⁷ However, alpha disintegrations are in fact remarkably easy to shield because of the particles' heavy mass and limited penetration — picture a minimal-range heavy missile stopped by a sheet of paper. Universal precautions generally suffice. Radium-223 is transportable worldwide in shielded, screw-cap vials. Unlike its older cousin, it rapidly decays into stable compounds — meaning that after several half-lives, one can discard any waste with ordinary trash. Logistically, alpha-emitter

Table 1. The Past, Present, and Future Role of Alpha Emitters in Medicine.*

Isotope	Half-Life	Application	Main Biodistribution	Comments	U.S. Clinical Trials
Radium-223	11.4 days	Cancer therapy	Bone	First alpha emitter to undergo phase 3 testing and receive FDA approval for clinical use in metastatic castration-resistant prostate cancer ⁶	Active but not recruiting: phase 2A trial in breast cancer (ClinicalTrials.gov number, NCT01070485) and two open phase 1–2A studies in metastatic castration-resistant prostate cancer (NCT01106352, in combination with docetaxel; and NCT01618370)
Radium-226	1601 yr	Cancer brachytherapy with sealed sources in needles (interstitial) and tubes (intracavitary) for implantation into tumors	Bone	First and only available brachytherapy source before 1950, when it was used by ophthalmologists, dermatologists, gynecologists, and radiologists; radiation poisoning detected in persons who painted watch dials with paint containing radium; many other medical reports of misplaced and mishandled sources	None
Thorium-232	14 billion yr; biologic half-life in bone is 22 yr	Contrast agent (thorium dioxide) popular for its radiopacity	Liver, spleen, lymph nodes, and bone	Fell out of favor in the United States in the 1950s because of increased risk of leukemias and liver hemangiosarcomas	None
Astatine-211	7.2 hr	Cancer therapy	Thyroid and liver	Deemed “most promising” alpha-particle therapy ⁸ because of relatively longer half-life than related isotopes, 100% alpha decay, and feasibility for imaging	None; closed in 2005: phase 1 trial of astatine-211–labeled antitenascin chimeric monoclonal antibody in resection cavities of primary and metastatic brain tumors (NCT00003461)
Bismuth-213	45.6 min	Cancer therapy, possible conditioning regimen in lieu of total-body irradiation in stem-cell transplantation	Kidneys	Preclinical studies suggest role for nononcologic use as radiolabel for antibody-guided treatment of microbial infections (including those caused by indwelling medical devices) and human immunodeficiency virus type 1	None; closed in 2009: phase 1–2 trial of sequential cytarabine and bismuth-213 labeled humanized anti-CD33 in advanced myeloid cancers (NCT00014495)
Actinium-225	10 days; but biologic half-life can be extended if this isotope is not bound to chelating agents	Cancer therapy	Bone and liver	Promising preclinical studies in leukemia and lymphoma, neuroblastoma, and breast, ovarian, and prostate cancer	Recruiting: phase 1 trial of actinium-225–labeled humanized anti-CD33 monoclonal antibody in advanced myeloid cancers (NCT00672165) and phase 1–2 trial of lintuzumab–actinium-225 with cytarabine in acute myeloid leukemia (NCT01756677)

* FDA denotes Food and Drug Administration.

therapy is feasible for most centers whose staff members are well-trained in radionuclide therapy as long as there is some initial investment to update existing safety procedures and to acquire alpha-tailored assay and survey devices, as well as an ongoing investment in training for radiation safety personnel.

As for patients' safety, Parker et al. report remarkable tolerability of radium-223 in a population that had a baseline risk of progressive complications from underlying disease.⁶ The decay kinetics of radium-223 and its use in patients with metastatic disease also suggest that the legacy of second cancers observed in the days of the "radium girls" (female factory workers who had radium poisoning in the early 20th century) and the common medical use of thorium dioxide (Table 1) will not be repeated.

In 1996, a workshop sponsored by the Department of Energy on the development of alpha emitters for medical use identified multiple priority areas for future clinical research, including applications for nonmalignant conditions such as immune disorders and degenerative joint disease.⁸ Astatine-211 and bismuth-213 were deemed the most promising agents at the time. Yet in 2013, barriers to their adoption remain. Few alpha emitters are actively being tested in the clinic, and these tests are limited to cancer trials (Table 1). Radionuclide therapy is not a new concept in oncology. The trick is to deliver the radiation dose to the right target with minimal collateral damage; the trick with antibody therapy is that target engagement on the cell surface is not always sufficient to have a cytotoxic effect. Radioimmunotherapy is a successful approach in cancer therapy that marries a homing antibody of choice to a lethal radioisotope. As newer targeting molecules emerge, we can envision alpha emitters as a potent partner to further enhance radioimmunotherapy and create the ultimate "smart bomb."

But questions certainly remain. Bone-seeking beta emitters such as phosphorus-32, strontium-89, and samarium-153 lexidronam have been tested, yet the alpha emitter is the only one to show a survival advantage. Is the higher relative biologic effectiveness of alpha particles the sole cause, or did differences in study design, patient selection, or isotope localization contribute? Although some gamma emission permits imaging of the whereabouts of radium-223,⁹

established and validated methods to quantify the dose delivered to the body and to each lesion are lacking.¹⁰ As compared with non-alpha emitters, alpha particles, which have high linear energy transfers and limited-range paths, necessitate a greater emphasis on elucidating their biodistribution and microdosimetry (the measurement of energy deposition and distribution at the cellular and subcellular levels after radiation exposure). Nonetheless, this study imparts some long-awaited momentum to research on the use of alpha emitters and shows an overall survival advantage with a compound that is safe and manageable for both patients and providers. Radium-223 will both complement and contend with existing therapies. While its most appropriate "fit" is actively investigated, the first-line role of taxanes in metastatic castration-resistant prostate cancer may be reexamined and the viability of alpha particles in medicine may be newly explored 115 years after their discovery.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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