Targeted α-Based Treatment of Metastatic Castration-Resistant Prostate Cancer: Revolutionizing Systemic Radiotherapy?

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Nuclear medicine treatment of cancer exploits the targeting of radiation through transporters or receptors on tumor cells. Building on this principle, the complexity of therapeutic radiopharmaceuticals varies from simple radioactive elements such as ^{131}I and ^{223}Ra to conjugated carrier molecules that can subsequently be radiolabeled, such as antibodies, peptides, and small molecules. It is not simple to achieve the unique promise of targeted systemic therapeutic radiopharmaceuticals to deliver this cytotoxic payload to the tumor while sparing normal tissues. The success or failure of this approach is determined by a complex set of factors, including the affinity of the carrier molecule, the stability with which the radionuclide–carrier complex is bound, pharmacokinetics, biodistribution, receptor expression, and the sensitivity of the tumor cells and normal organs to radiation (*1*).

For many decades, only β-emitting radionuclides were used for targeted systemic radiotherapy, starting with ^{131}I treatment of differentiated thyroid cancer more than 70 y ago. Many years later, a range of therapeutic radiopharmaceuticals was developed using small molecules, peptides, antibodies, and particles radiolabeled with ^{131}I, ^{90}Y, and ^{177}Lu. Recently, the extraordinary clinical benefit of ^{177}Lu-labeled DOTA-octreotate in patients with neuroendocrine tumors was reported (*2*). As compared with the standard of care, ^{177}Lu-DOTA-octreotate resulted in an impressive gain in progression-free and overall survival for patients with metastatic neuroendocrine tumors.

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α-emitting radionuclides have characteristics that are considered favorable for therapy. The ultrashort range and the high-linear-energy transfer resulting in double-strand DNA breaks in adjacent cells after a single hit are likely when the decay occurs nears the tumor cell nucleus. To stop this from happening in normal tissues sufficiently to prevent detrimental side effects, several challenges need to be overcome. First, the radiopharmaceutical needs to be stable in vivo, so that the complex carries the radionuclide to the target. Thus, high-quality radiochemistry is mandatory. Second, preferential targeting of tumor cells with rapid blood clearance is needed to prevent long circulation times. Third, accumulation needs to be low in normal tissues in relation to targeted tumor cells, especially when the normal tissues are radiosensitive. Until recently, α-emitters were used only in an experimental setting, without achieving widespread clinical utility. The first α-emitter that proved to be successful was ^{223}Ra, which is now globally used for the treatment of patients with bone metastases from castration-resistant prostate cancer (mCRPC) (*3*). Analogously to β-emitting radioiodine in thyroid cancer, the simple radioactive α-emitting element ^{223}Ra preceded the application of more complex radiolabeled α-emitters. In parallel to the introduction of ^{223}Ra treatment for mCRPC, a second major development occurred in the area of molecular imaging of prostate cancer. Prostate-specific membrane antigen (PSMA)–binding ligands radiolabeled with ^{68}Ga for PET/CT proved to be successful in delineating prostate cancer metastases, showing high target–to–normal tissue uptake ratios as early as 1 h after injection (*4*). The use of ^{68}Ga-PSMA is being rapidly adopted, although sufficient evidence-based research to support its utility is lacking. The successful imaging of mCRPC by ^{68}Ga-PSMA immediately sparked research on the theranostic approach, selecting those patients with detectable metastases on ^{68}Ga-PSMA PET/CT for treatment with ^{177}Lu-PSMA (*5*). Although the data are preliminary, and conclusive trials with relevant clinical endpoints are pending, ^{177}Lu-PSMA holds the promise of success similar to that of ^{177}Lu-DOTA-octreotate, as 60%–70% of patients respond to ^{177}Lu-PSMA treatment. However, concerns about downregulation of androgen receptor signaling and PSMA have been raised, as well as about heterogeneous PSMA expression.

In this issue of *The Journal of Nuclear Medicine,* Kratochwil et al. report for the first time the results of compassionate-use treatment with the α-emitter ^{225}Ac radiolabeled to the PSMA-617 molecule in two heavily pretreated patients with mCRPC for whom other options were no longer available (*6*). Despite being refractory to most of the currently available treatment options for this disease, including ^{177}Lu-PSMA-617, the patients went into a complete PSA remission and a complete imaging remission after treatment with this α-particle–emitting radiopharmaceutical, described as ^{225}Ac-PSMA-617. Despite previous chemotherapy exposure and extensive bone metastases, which can take up large amounts of radiopharmaceutical, side effects to bone marrow were remarkably mild, as no significant hematologic

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toxicity was observed. The most significant side effect was severe xerostomia as the radiopharmaceutical was taken up by PSMA-expressing salivary glands, which are heavily targeted and subsequently become dysfunctional. Strategies to abrogate this toxicity are required.

Although Kratochwil et al. reported the treatment of only two patients, comparison comes to mind with the first report, in 2001, of the remission induced in a single gastrointestinal stromal tumor patient treated with imatinib (*7*). Development of imatinib and subsequent targeted therapies has had a major impact on the treatment of cancer. The article by Kratochwil et al. reports on the use of ^{225}Ac-PSMA-617 as last-resort salvage treatment, which is compliant with the updated Declaration of Helsinki on unproven interventions in clinical practice and with regulations in Germany, where these treatments were performed. Prospective studies are now urgently required to further investigate ^{225}Ac-PSMA-617 in mCRPC patients. The initial need is for dose-finding studies to further delineate tolerability, cumulative toxicity, recommended dosing and scheduling, optimal treatment duration, and safety in order to allow the rapid and seamless progression—to phase II clinical studies with relevant oncologic endpoints—that is needed to proceed beyond niche application in incidental patients. If the antitumor activity described to date is confirmed in a larger prospective trial, we envision this to be a new class of agents for the prostate cancer armamentarium, with potential for treating not only late-stage disease but also less advanced disease. ^{68}Ga-PSMA PET/CT, which could serve as the key predictive biomarker for patient selection for ^{225}Ac-PSMA-617, also requires further evaluation in these trials.

Obviously, there are many challenges ahead. For example, a guaranteed supply of the cyclotron product ^{225}Ac may be an issue. Legislation for clinical use of α-emitters may not be straightforward in every country, although with the approval of ^{223}Ra, much of the groundwork has been done. Another challenge is the significant financial investment that will be required to advance this clinical drug development program, although expedited approval may be feasible if antitumor activity is maintained. Protocol development will also require careful consideration. To make informed decisions, we need predictive biomarkers to evaluate in which subset of patients ^{225}Ac-PSMA-617 will work. Although the companion diagnostic ^{68}Ga-PSMA is likely to be important, tumor biology must also be considered; we will need an understanding of whether specific prostate cancer subtypes, such as those with DNA repair defects, are more sensitive to selective tumor cell killing by α-particle–emitting radiopharmaceuticals. We also need to know the relevance of prostate cancer cells lacking PSMA expression. Because the path length of α-radiation is just a few micrometers, we will not be able to exploit the bystander effect from targeted PSMA-positive tumor cells toward PSMA-negative tumor cells as we do when using β-emitters. This will raise the question of whether to develop ^{225}Ac-PSMA-617 as a stand-alone agent or in combination with other (approved or novel) anticancer drugs. The fact that PSMA expression is driven by activity of the folate-hydrolase 1 gene, which is controlled by androgen receptor signaling, will provide an option for combined treatment approaches. We need to evaluate whether the antitumor activity of such novel therapeutics will be increased or decreased by agents targeting androgen receptor signaling, particularly in light of concerns that some prostate cancer cells may be more likely to lose androgen receptor expression after next-generation endocrine treatments such as abiraterone and enzalutamide (*8*). Moreover, we need to evaluate the intratumoral inflammatory response—induced in part by androgen deprivation—and its impact on radiation effects, because studies indicate that myeloid-derived suppressor cells, for example, can protect prostate cancer cells from anticancer agent cytotoxicity (*9*).

In conclusion, Kratochwil et al. report preliminary but important results indicating that α-particle–based systemic radiotherapy with ^{225}Ac-PSMA-617 may have substantial therapeutic potential with a favorable therapeutic window. Although it is too early to label ^{225}Ac-PSMA as a breakthrough for treatment of patients with mCRPC, the impressive responses in patients with end-stage disease should spark major efforts to perform further clinical studies with α-emitting radiopharmaceuticals. This area of study should be given the highest priority so that its full potential can be assessed and the evidence generated to enable rapid registration of this class of cancer therapeutics. Clinical studies on this topic must be accompanied by appropriate translational research so that we can better understand the effects of ^{225}Ac-PSMA-617 on a cellular level, maximize antitumor activity, and—what is most important—improve the clinical care of patients with this most common of male cancers.

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