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Invited Perspective

Targeted alpha-based treatment of metastatic castration-resistant prostate cancer patients: 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 I-131 and Ra-223 to conjugated carrier molecules such as antibodies, peptides and small molecules, which can subsequently be radiolabeled. The unique promise of targeted systemic radiotherapy with therapeutic radiopharmaceuticals to delivery this cytotoxic payload to the tumor, while sparing the normal tissues is not trivial to achieve. Affinity of the carrier molecule, stability of the binding of the radionuclide-carrier complex, pharmacokinetics, biodistribution, receptor expression and sensitivity of the tumor cells and of normal organs to radiation present a complex set of factors that determine success or failure of this approach [1].

For many decades, only beta-emitting radionuclides were used for targeted systemic radiotherapy, starting with I-131 treatment of differentiated thyroid cancer more than 70 years ago. Many years later, a range of radiopharmaceuticals was developed using small molecules, peptides, antibodies and particles radiolabeled with I-131, Y-90 and Lu-177 for therapy. Very recently, the extraordinary clinical benefit of Lu-177 labeled DOTA-Octreotate in patients with neuroendocrine tumors was reported [2]. As compared to standard of care, Lu-177-DOTA-Octreotate resulted in an impressive gain of PFS and OS of patients with metastatic neuroendocrine tumors.

Alpha-emitting radionuclides have characteristics that are considered very favorable for therapy. The ultra-short 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 prevent this happening in normal tissues sufficiently to prevent detrimental side effects, a number of challenges need to be overcome. First of all, the radiopharmaceutical needs to be stable *in vivo*, so that the complex carries the radionuclide to the target. Thus, high quality radiochemistry is mandatory, Secondly, preferential targeting of tumor cells with rapid blood clearance is needed to prevent long circulation times. Thirdly, accumulation in normal tissues needs to be very low in relation to tumor cell targeting, especially when these tissues are radiosensitive. Until recently, alpha-emitters were only used in an experimental setting, but never achieved widespread clinical utility. The first alpha-emitter that proved to be successful was Ra-223, which is now globally used for the treatment of patients with bone metastases from castration resistant prostate cancer (CRPC) [3]. Analogously to beta-emitting radioiodine in thyroid cancer, the simple radioactive alpha-emitting element Ra-223 preceded the application of more complex radiolabeled alpha-emitters. In parallel to the introduction of Ra-223 treatment for mCRPC, a second major development occurred in the area of molecular imaging of prostate cancer. PSMA-binding ligands radiolabeled with Ga-68 for PET/CT proved to be very successful to delineate prostate cancer metastases with very high target-to-normal tissue uptake ratios as early as 1-hour after injection [4]. The use of Ga-68-PSMA is being rapidly adopted, although sufficient evidence-based research to support its utility is

lacking. The successful imaging of mCRPC by Ga-68-PSMA immediately sparked research on the theranostic approach, selecting those patients with detectable metastases on Ga-68-PSMA PET/CT for treatment with Lu-177-PSMA [5]. Although the data are preliminary, and conclusive trials with relevant clinical endpoints are pending, Lu-177-PSMA holds the promise of success similar to Lu-177-DOTA-Octreotate, as 60-70% of patients respond to Lu-177-PSMA treatment although concerns about down-regulation of androgen receptor signaling and of PSMA, and of heterogeneous PSMA expression have been raised.

In this issue of The Journal of Nuclear Medicine, Kratochwil et al. report for the first time results of treatment on the basis of compassionate use with the alpha-emitter Ac-225 radiolabeled to the PSMA-617 molecule in two very heavily pretreated patients with mCRPC for whom other options were no longer available [6]. Despite being refractory to most, currently available treatment options for this disease, including Lu-177-PSMA-617, patients went into a complete PSA and complete imaging remission following treatment with this alpha-particle emitting radiopharmaceutical, described as Ac-225-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 hematological 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 2 patients, comparison comes to mind with the first report in 2001 of the remission induced in a single GIST patient treated with imatinib [7]. Development of imatinib and subsequent targeted therapies have had a major impact on the treatment of cancer. This manuscript reports on, last resort salvage Ac-225-PSMA-617 treatment, which is compliant with the updated Declaration of Helsinki on Unproven Interventions in Clinical Practice and in accordance with regulations in Germany, where these treatments were performed. Prospective studies are now urgently required to further investigate Ac-225-PSMA-617 in mCRPC patients. First of all, dose-finding studies are now urgently needed to further delineate tolerability, cumulative toxicity, recommended dosing and scheduling as well as optimal treatment duration, and safety in order to allow the rapid and seamless progression to Phase II clinical studies with relevant oncological end points in order 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 not only for treating late stage disease but also less advanced disease. Ga-68-PSMA PET/CT which could serve as the key predictive biomarker for patient selection for Ac-225-PSMA-617 also requires further evaluation in these trials.

Obviously, there are many challenges ahead. First of all, a guaranteed supply of the cyclotron product Ac-225 may be an issue. Legislation for clinical use of alpha-emitters may not be straightforward in every country, although much of the groundwork has been done after the approval of Ra-223. Last but not least, significant financial investments will be required to advance this clinical drug development program although expedited approval may be feasible if this 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 Ac-225-PSMA-617 will work. While the companion diagnostic Ga-68-PSMA is likely to be important, tumor biology must also be considered and an understanding of whether specific prostate cancer subtypes, such as those with DNA repair defects, are more sensitive to selective tumor cell kill by alpha-particle emitting radiopharmaceuticals will need evaluated. Furthermore, we also need to know about the relevance of prostate cancer cells lacking PSMA expression. As the path length of alpha-radiation is just a few um, there will not be much of a bystander effect from targeted PSMA-positive tumor cells towards PSMA-negative tumor cells, which we do exploit when using beta-emitters. This will raise the question whether to develop Ac-225-PSMA-617 as a stand-alone or in combination with other (approved or novel) anticancer drugs. As PSMA expression is driven by activity of the folate-hydrolase 1 (FOLH1) gene, which is controlled by androgen-receptor signaling, this provides options for combined treatment approaches. It will be necessary to evaluate if these novel therapeutics will have their antitumor activity 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, study of the intratumoral inflammatory response, induced in part by androgen deprivation, and its impact on radiation effects needs evaluation since studies indicate that for example myeloid derived suppressor cells can protect prostate cancer cells from anticancer agent cytotoxicity [9].

In conclusion, Kratochwil et al. report very preliminary but important results indicating that alpha-particle based systemic radiotherapy with Ac-225-PSMA-617 may have substantial therapeutic potential with a favorable therapeutic window. Although it is too early to label Ac-225-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 alpha-emitting radiopharmaceuticals. This should be given the highest priority to assess their full potential and to generate the evidence required for rapid registration of this class of cancer therapeutics. These clinical studies must be accompanied by appropriate translational research to better understand the effects of Ac-225-PSMA-617 on a cellular level, maximize antitumor activity and most of all improve the clinical care of this commonest of male cancers.

REFERENCES

[1] Koppe MJ, Postema EJ, Aarts F, Oyen WJ, Bleichrodt RP, Boerman OC. Antibody-guided radiation therapy of cancer. Cancer Metastasis Rev 2005; 24: 539-567.

[2] Strosberg JR, Wolin EM, Chasen B, et al. ^{177}Lu-Dotatate significantly improves progression-free survival in patients with midgut neuroendocrine tumours: Results of the phase III NETTER-1 trial. Eur J Cancer 2015; 51 Suppl.3: S710.

[3] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369: 213-223.

[4] Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the ^{68}Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2015; 42: 197-209.

[5] Baum RP, Kulkarni HR, Schuchardt C, et al.^{177}Lu-Labeled Prostate-Specific Membrane Antigen Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy. J Nucl Med 2016; 57: 1006-1013.

[6] Kratochwil C, Bruchertseifer F, Giesel FL, et al. ^{225}Ac-PSMA-617 for PSMA targeting alpha-radiation therapy of patients with metastatic castration-resistant prostate cancer. J Nucl Med 2016; 57: xxx – xxx.

[7] Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. N Engl J Med 2001; 344: 1052-1056.

[8] Watson PA, Arora VK, Sawyers CL. Emerging Mechanisms of Resistance to Androgen Receptor Inhibitors in Prostate Cancer. Nat Rev Cancer 2015; 15: 701–711.

[9] Di Mitri D, Toso A, Chen JJ, et al. Tumour-infiltrating Gr-1+ myeloid cells antagonize senescence in cancer. Nature 2014; 515: 134-137.

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