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EDITORIAL COMMENTARY

Value proposition of PSMA-targeted α–particle radioligand therapy in metastatic prostate cancer

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Theranostics is currently experiencing a renaissance since the early days of radioiodine use in thyroid diseases. While there have been prior clinical platforms for theranostics (e.g., lymphoma, neuroblastoma), the recent regulatory approval and reimbursement of paired agents for somatostatin receptor-targeted theranostics of neuroendocrine tumors has helped to enrich the field [1]. Exciting developments are currently underway in theranostics of metastatic castrate-resistant prostate cancer (mCRPC), with prostate-specific membrane antigen (PSMA) as the biological target. Despite some limitations with nonspecificity, small molecule inhibitors binding to the external moiety of PSMA and radiolabeled with ^{68}Ga- (e.g. PSMA-11, PSMA-617, PSMA I&T) or ^{18}F- (e.g. DCFPyL, PSMA-1007) have demonstrated excellent diagnostic imaging performance and competitive advantage over other non-PSMA based radiotracers [2]. When radiolabeled with β-emitters (e.g., ^{177}Lu, ^{131}I) or α-emitters (e.g., ^{225}Ac, ^{213}Bi), particular PSMA-based agents can also be used for targeted radiotherapy of the same metastatic lesions that are identified by the imaging companion agent realizing the bidirectional "see & treat" concept [3–9].

Most clinical experience with radioligand therapy in mCRPC has been with ^{177}Lu-PSMA-617 for compassionate care in heavily pre-treated patients [10]. Even in this challenging clinical situation, remarkable efficacy and safety has been demonstrated. Nearly 50% of patients show PSA decline of $\geq$ 50% after repeated cycles of therapy, although about a third of patients may present with delayed response to additional cycles of therapy after initially showing no response to the first cycle. The adverse hematological toxicities are generally mild and manageable. Nephrotoxicity, if it occurs, is low grade. Xerostomia appears to be the most noteworthy toxicity, but is again generally mild or transient. Limited studies also suggest outcome benefit in terms of improved progression-free survival and overall survival.

It has been almost 20 years since the demonstration of efficacy with α-particle emitting monoclonal antibody ^{213}Bi-J591 therapy in athymic nude mouse xenograft models of human prostate cancer [11]. Recently, a few pilot human studies have emerged using ^{225}Ac (half-life 9.9 d) or ^{213}Bi (half-life 46 min) with PSMA-617. A clinical case report from South Africa showed favorable response to treatment with ^{213}Bi-PSMA-617 in a patient with progressive mCRPC [12]. In a dosimetry study of three patients with mCRPC, the German investigators concluded that ^{213}Bi-PSMA-617 has higher perfusion-dependent off-target radiation, and would be "second-choice" compared to ^{225}Ac-PSMA-617 [13].

The reports from Heidelberg with the use of ^{225}Ac-PSMA-617 have been quite encouraging [14]. In one clinical case, these investigators showed remarkable PSA decline and disappearance of lesions on ^{68}Ga-PSMA-11 PET scan in a mCRPC patient who was treated with three cycles of ^{225}Ac-PSMA-617 after initial unsuccessful therapies with two cycles of ^{177}Lu-PSMA-617 [15]. In their dosimetry studies, Kratochwil et al. suggest an upper limit dose of 100 kBq/kg administered bimonthly as the recommended therapy dose and schedule for ^{225}Ac-PSMA-617, based upon development of significant salivary toxicity (dry mouth) and a case of lacrimal gland toxicity (dry eye) at higher doses [16]. However, there were no renal or liver toxicities.

While the results of the previous limited studies with ^{225}Ac-PSMA-617 have been promising when used in heavily pre-treated mCRPC patients, in this issue of the journal, the group from South Africa reported their experience with ^{225}Ac-PSMA-617 in 17 patients with chemotherapy-naïve mCRPC [17]. In a deescalating dose schedule administered every 2 months starting from an initial dose of 8 MBq, these

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investigators observed PSA declines ≧ 90% from pre-treatment levels in 82%, and > 50% decline in lesion avidity for ^{68}Ga-PSMA-11 in 88% of patients. Remission was achieved in 41% of patients over a 12-month follow-up period. Only one patient failed the treatment. The de-escalation dosing schedule was apparently responsible for limiting the salivary gland toxicity to grades 1 or 2 in all patients. Other than one patient with one functional kidney with baseline insufficiency and another patient with anemia at baseline who had further decline in hemoglobin level after the first cycle of radioligand therapy, no statistically significant changes were noted in blood counts, or renal and hepatic panels.

This retrospective pilot study by Sathekge and colleagues from the University of Pretoria had two interesting features. First, the patient cohort declined chemotherapy and thus was chemotherapy-naïve. It has been suggested previously that in order to realize the potential of PSMA radioligand therapy in improving patient outcome significantly, it should be investigated earlier in the course of metastatic disease rather than late in the disease process when all other therapies have been exhausted. The additional unique circumstance of the South African public hospitals, in which abiraterone and enzalutamide are unavailable, provided an opportunity to study patients who would have probably been first treated with these anti-androgen agents rather than first-line PSMA radioligand therapy. Second, a strategy of deescalating dose schedule of ^{225}Ac-PSMA-617 was employed in order to mitigate the problem of radioligand therapy induced xerostomia, which seemed to be beneficial. If confirmed in other studies, this strategy would probably be preferable to intrusive interventions such as botulinum toxin injection into the salivary glands or sialendoscopy with dilatation in combination with saline irrigation and steroid injection [18, 19].

Many questions still remain that will need answers in the coming years before PSMA radioligand therapy (with β-emitters, α-emitters, or as cocktail or in sequence) can become approved, reimbursed, and standard of care in patients with metastatic prostate cancer. The notion is generally held that the relatively longer range and lower energy of β particles are effective in affecting macrometastases, while substantially shorter range and higher energy of α particles are more effective in treating micrometastases. However, the limited current evidence demonstrating effective α-particle therapy of macrometastases refractory to β-particle therapy suggests that this view is probably too simplified, and more complex biological interactions may be at play in the tumor microenvironment.

Randomized clinical trials are needed in comparative effectiveness of PSMA radioligand therapy versus currently approved treatments, either as single, combination, or sequential agents. The recent experience with excess fractures and deaths in the ^{223}Ra dichloride plus abiraterone acetate plus prednisone/prednisolone arm versus placebo plus abiraterone acetate plus prednisone/prednisolone arm in asymptomatic or mildly symptomatic chemotherapy-naive patients with bone predominant mCRPC (ERA-223) demonstrated that combinations of cancer drugs, although they may potentially be synergistic in efficacy, may not always be safe [20]. Availability and accessibility to α-emitters will also be crucial. While PSMA radioligand therapy is not curative and appropriate patient selection is essential, nevertheless, it is anticipated that the current momentum with PSMA radioligand therapy will accelerate, based on the impressive value proposition that it appears to offer to the management of patients with metastatic prostate cancer and possibly other PSMA-overexpressing malignancies.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest. This article does not contain any studies with human participants or animals performed by the author.

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