Prostate-specific Membrane Antigen: Alpha-labeled Radiopharmaceuticals

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Novel prostate-specific membrane antigen (PSMA) ligands labeled with α-emitting radionuclides are sparking a growing interest in prostate cancer treatment. These targeted alpha therapies (TATs) have attractive physical properties that deem them effective in progressive metastatic castrate-resistant prostate cancer (mCRPC). Among the PSMA TAT radiopharmaceuticals, [225Ac]Ac-PSMA has been used extensively on a compassionate basis and is currently undergoing phase I trials. Notably, TAT has the potential to improve quality of life and has favorable antitumor activity and outcomes in multiple scenarios other than in mCRPC. In addition, resistance mechanisms to TAT may be amenable to combination therapies.

Key points

- The physical characteristics of α-particles allow for the better radiobiological efficiency of prostate-specific membrane antigen radiopharmaceuticals that emit α-particles. They have a position in the progressive metastatic castrate-resistant prostate cancer because of their direct and indirect cytotoxic effects on DNA and organelles through reactive oxygen species, bystander, and abscopal immune-mediated pathways.
- Whether the metastatic prostate cancer is hormone-sensitive or castration-resistant, targeted-alpha therapy (TAT) has shown strong antitumor effectiveness, long-term survival, and an improvement in quality of life in patients at different stages of the disease.
- The salivary glands are the dose-limiting organs. Salivary gland toxicity secondary to TAT may manifest with indirect clinical symptoms such as loss of appetite impacting on the quality of life. Various mitigatory measures have been partially effective in reducing its incidence.

Introduction

Despite advances in diagnosis and treatment, prostate cancer remains one of the leading causes of death among men.[1] While there has been significant improvements in available treatments and patient outcomes in recent years, improvements in survival in patients with metastatic castrate-resistant prostate cancer (mCRPC) remains an unmet need.

Prostate-specific membrane antigen (PSMA) is an integral protein overexpressed by prostate cancer cells to a greater extent in metastatic and castrate-resistant prostate cancer (CRPC). Among therapeutic agents, the β-emitting radiopharmaceutical [^{177} Lu]Lu-PSMA-617 has undergone a phase 3 trial. The results of which have led to the approval of [^{177} Lu]Lu-PSMA-617 under the trade-name [^{177} Lu]Lu-PSMA-617 (Pluvicto- Novartis Holding AG. Postfach Basel, Switzerland).[2,3] However, a significant proportion of patients may not respond and most eventually demonstrate progression on [^{177} Lu]Lu-PSMA-617. This has opened a window for an extensive investigation of PSMA-based targeted-alpha therapy (TAT) in mCRPC either in lieu of [^{177} Lu]Lu-PSMA-617 in patients who are not candidates or as an alternative in patients who are resistant to [^{177} Lu]Lu-PSMA-617.

Prostate-specific membrane antigen

PSMA is a type II transmembrane glycoprotein receptor that is encoded by the folate hydrolase 1 gene located on the short arm of chromosome 11. It has been a “game changer” in the management of prostate cancer as a target of both imaging and therapeutic agents.[4] Although the name implies that it is found only in prostatic tissue, it is not specific to prostatic tissue since it has been isolated in various other tissues such as salivary glands, glial cells, enterocytes, kidneys, and importantly in the neovasculature of multiple other solid tumors. Structurally, PSMA consists of approximately 750 amino acids, with 19–amino-acid intracellular domain, a 24–amino-acid transmembrane domain, and a large, 707–amino-acid, extracellular domain. PSMA possess enzymatic functions that include glutamate carboxypeptidase II and folate hydrolase activity.

In normal prostatic tissue, PSMA is expressed in the apical surface rather than the basal endothelial surface. It is upregulated more than 100 to 1000 times in prostate cancer. The upregulation is inversely related to the androgen depletion correlating with the high levels of expression in CRPC.[5] PSMA has been implicated in the metabolism, proliferation, and metastasis of prostate cancer in preclinical investigations. One of the proposed mechanisms is dysregulating the β1-integrin/type I insulin-like growth factor receptor axis, resulting in a shift in signaling from the less aggressive mitogen-activated protein kinase-extracellular signal-regulated kinases 1 and 2 pathways to the prosurvival protein kinase AKT/phosphatidylinositol 3-kinase pathway.[6,7] Once a ligand binds to PSMA, the ligand–PSMA complex is internalized by clathrin-dependent endocytosis, making this a valuable tool for the delivery of both diagnostic and therapeutic agents.

Alpha-emitting radionuclides for prostate-specific membrane antigen: physics and radiobiology

The favorable physical features of α-emitting radionuclides have sparked interest in them for PSMA TAT. As early as the 1950s, Zirkle and colleagues demonstrated that with the same dose rates, α-particles are more deleterious compared to other types of ionizing radiation. They explained this to be due to the high linear energy transfer (LET) defined as the amount of energy deposited per unit length by ionizing radiation.[8] This high LET is due to the physical property of the α-particles, which is a heavy helium nucleus with a double-positive charge ($^{4}He^{2+}$). It has short path lengths of up to 100 µm in water equivalent tissues and 40 µm in bone, which translates to LET of 50 keV/µm to a maximum of 230 keV/µm at the Bragg Peak.[9]

The α-particles have several advantages that contribute to an increased cytotoxicity relative to other forms of radiation. Deoxyribonucleic acid (DNA) has generally been regarded as the most important target of ionizing radiation-mediated cytotoxicity. Ionizing radiation can cause direct or indirect damage to DNA. Direct damage as the name implies is mediated by direct transfer of energy to the DNA. Reactive oxygen species (ROS) formed by ionization of water mediate indirect DNA damage. The short path lengths and the high LET α-particles effect more direct DNA damage breaks compared to indirect DNA damages. This is independent of perfusion making α-radiation more effective in hypoxic tissues. In addition, α-particles induce more double-strand breaks that are more difficult to repair compared to the more common single-strand DNA breaks with β-emitting radiation.[10] Ideally, the α-particles induce DNA damage within the cancerous cell without cross-over to the adjacent cells minimizing side effects to these tissues. Therefore, considering all these properties, it becomes suitable for the treatment of small metastatic lesions and lesions resistant to β-emitting radiation. Furthermore, α-radiation also provides extra advantages that ultimately causes cytotoxicity to cancerous cells that are not exposed directly to α-radiation. These cells may be distant or near the irradiated cell. If the cells are adjacent to the irradiated cell, these effects are known as bystander effects, whereas systemic effects are immune-mediated and are known as abscopal effects. Cytotoxic and genotoxic modifications (DNA damage, chromosomal aberrations) in cells that are in the proximity of irradiated cells, but that are not traversed by particles characterize these bystander effects. Irradiated cells release damage-associated molecular patterns that induce a local inflammatory response. The recruitment of antigen-presenting cells may lead to activation of the adaptive immune response with T-cell activation.[11,12]

The cytotoxicity of α-particles has also been shown to be dependent on the damage of other cellular components in addition to DNA damage. These include the cell membrane, cytosol, and other organelles. As ionizing radiation traverses the cell membrane, cell membrane lipids may be disrupted. Mitochondria, a cytosolic organelle, possess DNA which can be damaged by α-particles affecting mitochondrial functions. Disruption of mitochondrial function following irradiation contributes to the persistence of oxidative stress through dysfunction of respiratory complex I. This leads to an intracellular increase in ROS production and mitochondrial DNA damage. Organelle interaction has also been implicated in bystander effects; however, this is beyond the scope of this review.[12,13]

The α-emission is a highly energetic process associated with the recoil of the daughter radionuclide. Due to the momentum conservation law, part of the decay energy is transferred to a daughter nucleus. This recoil may lead to radiolysis of the radiopharmaceutical, which may lead to the decoupling of the daughter radionuclide from the radiopharmaceutical. The result of this recoil is 2 fold and dependent on the exact location of the parent radionuclide. If this is intracellular, the recoil of the daughter radionuclide may add to the overall cytotoxicity if retained within the tumor. If this occurs extracellularly, the daughter radionuclide that is in circulation might be hazardous to healthy organs like the kidneys. This is especially important in in vivo radionuclide generators that produce radioactive daughter nuclides. The use of single α-emitting radionuclides has been one of the proposed ways to address the recoil effect. Another approach is the use of a ligand with fast tumoral uptake and fast clearance of the unbound radioligand relative to the radionuclide from the nontarget organ. The faster uptake allows the emission and retention of the daughter radionuclide intratumorally with no release of radioactive daughter nuclides into the circulation. Other approaches have been intratumoral injection of the radionuclide and the encapsulation in nanocarriers.[14,15]

As discussed later, [^{225} Ac]Ac half-life of 9.9 days is an example of an in vivo radionuclide generator, emitting multiple α-particles through various daughter radionuclides one of which is [^{213} Bi]Bi. The rapid tumor approach with small PSMA molecules has been used to reduce the untoward effects of the recoil effect. This has also overcome the limitation of the relatively short half-life of [^{213} Bi]Bi (46 minutes). More importantly, the high number of α-particles emitted if [^{225} Ac]Ac decays implies more cytotoxicity relative to the use of [^{213} Bi]Bi, an advantage of in vivo generators.[16,17]

Despite these attractive properties, only a few α-emitting radionuclides have desirable properties suitable for PSMA-targeted therapy. [^{225} Ac]Ac, [^{213} Bi]Bi, [^{149} Tb], [^{212} Pb/ ^{212} Bi], [^{211} At]At, and [^{227} Th]Th (Table 1 *: summary of their physical properties*), have been complexed to PSMA inhibitors and evaluated in preclinical and clinical studies for their efficacy and safety in the treatment of mCRPC.[18] Among these, [^{213} Bi]Bi and [^{225} Ac]Ac are the most extensively evaluated clinically due to the challenges associated with preclinical to clinical translation as discussed in later section.[19]

Table 1. Summary of alpha-emitting radionuclides suitable for targeted alpha therapy for prostate cancer

Radionuclide	**Half-life**	**Emitted Particles**	**Total α-energy Emitted per decay (MeV)**	**Range in tissue (μm)**	**LET (keV/μm)**	**Preclinical/Clinical**
[^{225} Ac]Ac	9.9 d	4α, 2β $^{-}$	27.9	47–85	61–230	Preclinical/clinical
[^{213} Bi]Bi	45.6 min	2α, 2β $^{-}$	8.5	40–100	65–230	Preclinical/clinical
[^{212} Pb]Pb/[^{212} Bi]Bi	10.6 h	1α, 2β $^{-}$	7.9	40–100	61–230	Preclinical
[^{149} Tb]Tb	4.1 h	1α, 1ϵ/2ϵ; 1β $^{+}$/2β $^{+}$/	0.7	25	140	Preclinical
[^{227} Th]Th	18.7 d	4α, 2β $^{-}$	32.8	50–70	71–230	Preclinical
[^{223} Ra]Ra	11.4 d	4α, 2β $^{-}$	26.8	46–70	71–230	Preclinical

[^{211}At]At	7.2 d	1α, 1ϵ	6.9	55–80	71–230	Preclinical

[^{149}Tb]Tb

[^{149} Tb]Tb is a radiolanthanide with a physical half-life of 4.1 hours and an attractive decay scheme. It consists of multiple different particulate and nonparticulate radiation: α-particles (3.97 MeV, 16.7%), electron capture (76.2%), positron emission (7.1%), gamma rays (165 keV, 26.4%), and x-rays. This possibility of both single-photon emission computed tomography and PET imaging in addition to TAT allows for accurate retrospective dose estimations to plan future applications and minimize off-target toxicity.[18] It has been complexed to PSMA-617 and investigated preclinically. Umbricht and colleagues investigated TAT with [^{149} Tb]Tb-PSMA-617 in a PSMA mouse model. They demonstrated delayed tumor growth in the [^{149} Tb]Tb-PSMA-617 group compared to the control group, which was injected with normal saline. The downside was an increased radiation dose to the kidneys more than 10 times that of [^{177} Lu]Lu-PSMA-617.[20] The clinical translation of [^{149} Tb]Tb-PSMA-617 has been precluded by the limited supply and the difficulties of production and chemical separation. The high recoil energy causes radiolysis of the radiopharmaceutical leading to dissemination of these long-lived bone-seeking daughter radionuclides that eventually lead to increased bone-marrow and whole-body radiation dose.[21,22]

[^{212}Pb] Pb

[^{212} Pb] Pb is obtained from a [^{224} Ra]Ra/[^{212} Pb]Pb generator and has a half-life of 10.64 hours and is an in vivo α-particle emitting radionuclide generator. It decays to [^{212} Bi] Bi (half-life = 60.6 min) and [^{212} Po]Po (half-life = 0.3 μs). One αparticle is released in this process. One of its daughters [^{212} Bi]Bi has a half-life of 61 minutes which ultimately disintegrates to a stable [^{207} Pb]Pb after the release of one α-particle and one β-particle. [^{212} Pb] Pb with a longer half-life allows the use of reasonable activities and is more practical than using [^{212} Bi]Bi, which has a much shorter half-life requiring administration of much higher activities. [18] [^{212} Pb]Pb-PSMA-617 has initially demonstrated high kidney uptake. Although [^{212} Pb]Pb-NG001 has shown promising results with both higher tumoral uptake and less initial kidney uptake than [^{212} Pb]Pb-PSMA-617, the recoil energy is high. It is high enough to cause 36% of [^{212} Bi]Bi to dissociate from the radioligand imparting more radiation dose to the kidneys.[18, 23] However, the actual off-target radiation dose remains to be evaluated in humans. A phase I clinical trial Dose Escalation and Efficacy Study of [^{212} Pb]Pb-ADVC001 in Patients with Metastatic Castration-Resistant Prostate Cancer is currently ongoing [ClinicalTrials.gov ID NCT05720130].

[^{211}At]At

[^{211} At]At has its name derived from “astatos” meaning unstable and is often referred to as the rarest element on earth with only isotopes 214 to 219 found in the earth’s crust in equilibrium with uranium. Although this makes its availability an issue, its sustainability has been maintained by cyclotron production. Its radioactive decay follows a branched decay scheme with a half-life of 7.2 hours. The α-decay produces [^{207} Bi]Bi, a long-lived relatively stable nuclide emitting 1 α-particle meaning that it is not subject to recoil effects. The remaining 58.3% decay by electron capture to [^{211} Po]Po, a short-lived radionuclide (half-life

0.52 second) that produces characteristic x-rays (K x-rays). The K x-rays produced allow for in vivo imaging and quantification of [^{211} At]At radioactivity.[24,25] The major challenge with [^{211} At]At has been accumulation in renal tubules and late nephrotoxicity in preclinical studies.[26] However, multiple other precursors have been developed and have shown promising results with less off-target accumulation preclinically. These remain to be translated into clinical practice.[27,28]

[^{227} Th]Th

[^{227} Th]Th is a daughter radionuclide of [^{227} Ac]Ac. It decays with a half-life of 18.7 days to its daughter radionuclide [^{223} Ra]Ra by producing a single α-particle. [^{223} Ra]Ra decays to [^{207} Pb]Pb by producing multiple daughters, 5 α-particles and 2 β-particles. This makes [^{227} Th]Th-labeled conjugates subject to the recoil effect.[15,29] Hammer and colleagues demonstrated an antitumor effect on both in vitro and animal studies with a PSMA-targeted [^{227} Th]Th conjugate (PSMA-TTC) including models resistant to enzalutamide. The same group also demonstrated that darolutamide, an androgen receptor inhibitor, potentiates the antitumor efficacy of a PSMA-targeted PSMA-TTC by a dual mode of action in prostate cancer models. This evidence supported the ongoing safety and toxicity (phase I) studies in humans (NCT03724747).[30,31]

Clinical experience with targeted alpha therapy for prostate cancer

With the exception of the bone-seeking radiotracer [^{223} Ra]Ra, most of the clinical experience in prostate cancer is with [^{225} Ac]Ac and [^{213} Bi]Bi.

[^{213} Bi]Bi

[^{213} Bi]Bi is a product of [^{225} Ac]Ac an α/β emitter. It has a half-life of 46 minutes. About 97.8% is beta decay to [^{213} Po]Po, which is an α-emitter half-life of 4.2 microseconds. The other 2.2% of ^{213} Bi]Bi decays by α-emission to [^{209} Tl]Tl. Both [^{213} Po]Po and [^{209} Tl]Tl decay via [^{209} Pb]Pb to the long-lived [^{209} Bi]Bi. The total disintegration of [^{213} Bi]Bi consists of 92.7% α and the rest β-emission including decay of [^{209} Pb]Pb. The disintegration of [^{213} Po]Po contributes 98% to total α emission and is the main contributor of α-emission-mediated cytotoxicity. The coemission of 440 KeV gamma rays allows for in vivo imaging of [^{213} Bi]Bi biodistribution and the conduction of pharmacokinetic and dosimetric studies. [19]

Early in vitro and preclinical in vivo studies have used a monoclonal antibody J591, which targets the extracellular domain of PSMA, labeled with [^{213} Bi]Bi. Although effective cellular killing and prostate-specific antigen (PSA) decline were demonstrated, the inherent properties of monoclonal antibodies are not compatible with the very short half-life of [^{213} Bi]Bi of 46 minutes.[32] These properties which include long blood circulating time, decreased vascular permeability, and low infusibility within solid tumors effectively allow for extracellular disintegration of [^{213} Bi]Bi, which is detrimental to nontarget organs. Consequently, smaller PSMA inhibitors with fast uptake and more favorable pharmacokinetics for ^{213} Bi]Bi radiolabeling has been pursued.[33,34,35] No clinical studies have investigated [^{213} Bi]Bi-J591 in prostate cancer. Sathekge and colleagues reported the first-in-human therapeutic efficacy of [^{213} Bi]Bi-PSMA-617 in a patient with progressive mCRPC under

conventional therapy. The cumulative activity of 592 MBq administered over 2 cycles resulted in a good biochemical response with a PSA decline of more than 80%. In addition, [^{68} Ga]Ga-PSMA-11 PET/computed tomography (CT) done pretherapy and posttherapy showed a remarkable molecular imaging response. [36] Clinical pursuit of [^{213} Bi]Bi-PSMA-617 was halted after Kratochwil and colleagues demonstrated that [^{213} Bi]Bi-PSMA-617 had an inferior therapeutic index and increased radiation dose to the kidneys relative to [^{225} Ac]Ac-PSMA-617.[37]

[^{225} Ac]Ac

[^{225} Ac]Ac is obtained by chemical separation from [^{229} Th]Th, a product of fissile [^{223} U]U. [^{225} Ac]Ac has a relatively long half-life (9.9 days) and decays to [^{209} Bi]Bi via multiple short-lived radioactive daughter nuclei. Cumulatively, its decay produces 4 α-particles (energies ranging from 5.8 to 8.4 MeV and associated tissue ranges of 47–85 μm) and 2 β-particles of 1.6 and 0.6 MeV maximum energy. Nonparticulate radiation, which allows for in vivo biodistribution imaging and dosimetry studies is produced through the decay of the daughters [^{221} Fr]Fr and [^{213} Bi]Bi, which have gamma-emissions of 218 KeV and 440 KeV, respectively, with 11.6% and 26.1% probabilities.[19]

Among the developed Glu-urea ligands targeting PSMA, [^{225} Ac]Ac-PSMA-617 has been evaluated to a greater extent clinically and will be discussed extensively. In this publication, [^{225} Ac]Ac-PSMA refers to [^{225} Ac]Ac-PSMA-617 unless specified. Other groups have aimed to develop ligands with differing or favorable pharmacokinetics to [^{225} Ac]Ac-PSMA-617, with an increased therapeutic efficacy and a better side-effect profile. In their approaches, they have focused on the development of ligands with an increased albumin binding. Although radioligands such as [^{225} Ac]Ac-SibuDAB and [^{225} Ac]Ac-RPS-074 demonstrated reasonable efficacy and toxicity, they remain to be translated clinically. One of their properties that may preclude their clinical translation is their increased circulation times, which makes [^{225} Ac]Ac prone to recoil effects extracellularly resulting in more side-effects in humans.[38,39]

Despite the long existence of PSMA-I&T, limited data exist on the potential of [^{225} Ac] Ac-PSMA-I&T. Zacherl and colleagues were the first group to translate [^{225} Ac]Ac-PSMA-I&T clinically. The efficacy and toxicity profile was comparable to those of [^{225} Ac]Ac-PSMA-617.[40,41] [^{225} Ac]Ac-PSMA-I&T is currently undergoing a phase I/II study (NCT05902247 ; TATCIST: NCT05219500) and preliminary results are expected in 2024.

The clinical practice of [^{225} Ac] Ac-prostate-specific membrane antigen

Currently, much of the clinical practice of [^{225} Ac]Ac-PSMA has been extrapolated from lessons derived from [^{177} Lu]Lu-PSMA peptide radioligand therapy. Multiple national and international societies have published practice guidelines for [^{177} Lu]Lu-PSMA-617.[42,43,44]

Patient selection for [^{225} Ac]Ac-prostate-specific membrane antigen therapy

In general, [^{225} Ac]Ac-PSMA has been recommended for patients with histologically confirmed mCRPC who have progressed on conventional therapies and are either resistant or

have contraindications to [^{177} Lu]Lu-PSMA therapy. This was based on a first-in-human retrospective study by Kratochwil and colleagues. In 2 patients, with mCRPC who had progressed on [^{177} Lu]Lu-PSMA and another who had extensive bone marrow involvement in superscan pattern on PSMA-PET/CT imaging, they demonstrated complete remission after 3 cycles of [^{225} Ac]Ac-PSMA therapy. [45] Other studies have demonstrated that [^{225} Ac]Ac-PSMA therapy may also be indicated or beneficial in other patient groups as discussed in later sessions.

The appropriateness of [^{225} Ac]Ac-PSMA and any therapeutic regimen in oncology should be decided in a multidisciplinary team setting. Decision-making and baseline assessment of a patient for TAT should include assessment for PSMA expression and organ reserve. The relevant organs are the kidneys, liver, and bone marrow. The basis of this is due to the toxicity that has been demonstrated with both α-targeted and β-targeted therapies. Generally, the recommended tests include the following: estimated glomerular filtration rate (eGFR) greater than 30 mL/min, creatinine less than 2 fold upper limit of normal; liver enzymes less than 5 fold upper limit of normal and bone marrow function: hemoglobin level greater than 8 g/dL; platelet count greater than 75 × 10 ^{9} /L, and white cell count greater than 3 × 10 ^{9} /L. [42]

Sufficient PSMA expression determined from PSMA imaging is a prerequisite for consideration of [^{225} Ac] Ac-PSMA therapy. .Notably, prostate cancer like all tumors is a heterogeneous entity. Despite the presumption that PSMA is overexpressed in prostate cancer relative to normal tissues, some metastatic lesions may not express PSMA at all. Therefore, the use of a noninvasive, in vivo whole-body assessment tool becomes vital for decision-making, response prediction and reducing morbidity associated with unbeneficial treatment regimes.[46] Different groups have used different approaches; however, high PSMA uptake with no discordant lesion with no PSMA uptake favored good therapeutic outcomes. Visual and semiquantitative criteria have been used. Uptake more than the liver or salivary gland entails some of the criteria that have been applied in using visual analysis to determine [^{177} Lu] Lu-PSMA therapy eligibility. Other studies have used for [^{68} Ga]Ga-PSMA-11 PET/CT SUVmax (cutoffs ≥20; ≥1.5 × SUVmax of liver), SUVmean (≥10; average SUVmax: cutoffs 14.3), and for fluorinated PSMA (SUVmax ≥10 or > 1 × liver uptake).[3,47,48,49,50,51] A recent study by Hotta and colleagues used PSMA-PET tumor–to–salivary gland ratio to predict response to [^{177} Lu]PSMA radioligand therapy. However, the applicability of this with [^{225} Ac]Ac-PSMA therapy remains to be elucidated in light of the changes in salivary gland uptake with therapy.[52] It is worth mentioning that [^{18} F]FDG PET/CT has been used in some studies. Hofman and colleagues in both the TheraP and LuPSMA trial used [^{18} F]FDG PET/CT to evaluate for discordance uptake in tumor.[47,53] In our practice and in most other centers administering [225 Ac]Ac-PSMA for therapy for mCRPC across the world, [18 F]-FDG PET is not routinely used in the selection of patients for TAT.

Another factor that needs to be taken into consideration is the metastatic pattern as seen on PSMA imaging to decide on α-targeted or β-targeted therapy. In patients presenting with a super scan metastatic pattern on PSMA imaging, α-emitting radionuclides, in this case [^{225} Ac]Ac-PSMA, are preferable to reduce bone marrow toxicity. This is due to their shorter path lengths and their direct cytotoxic effects mainly limited to the cancerous cells as previously discussed.[45,54] , This also translates to patients with micrometastatic disease in which [^{177}

Lu]Lu-PSMA therapy may not be effective due to longer path length, a Bragg peak much further from the cancerous cell/DNA and low LET.[55]

Preparation for therapy administration

National guidelines on the handling of unsealed radioactive sources should be adhered to for TAT. Generally, this should be administered in a facility accredited for handling unsealed sources of radiation. At the minimum, the team should consist of a nuclear medicine physician, a medical physicist, a nuclear medicine nurse, and a nuclear medicine technologist. In our institution, this is generally administered on an outpatient basis. An individualized approach should be used in preparing a patient for [^{225} Ac] Ac-PSMA therapy. However, there are general baseline tests that should be obtained for efficacy and toxicity monitoring. These baseline blood tests should include the following.

- Serum PSA.
- Full blood count.
- Serum electrolytes, urea, and creatinine.
- eGFR.
- Liver function tests (LFTs).
- Dynamic renal scintigraphy is generally not indicated unless there is suspicion of obstructive uropathy either clinically or based on other tests that typically would have demonstrated a complete obstruction. [^{99m} Tc]Tc-MAG3 or other appropriate imaging agents may be used. Should an obstruction be present procedures to relieve obstruction are to be carried out before therapy to reduce the radiation dose to the kidneys.

Therapy administration

Kratochwil and colleagues recommended 100 kBq/kg body weight activities of [^{225} Ac]Ac-PSMA to be administered at 8 weekly intervals.[56] However, the administered activities should be based on tumor burden. In our center, we start with an empirical dose of 8 MBq, we then de-escalate or escalate based on the response and side effects in subsequent cycles.[57] For example, in patients who demonstrate partial response to [^{225} Ac]Ac-PSMA, the administered activity is reduced to 6 Mq, whereas those that either have stable disease or progression, the activity is maintained at 8 MBq. See Fig. 1 for an example of dose escalation and de-escalation in a patient with metastatic prostate cancer. The administration intervals are, however, similar to those of Kratochwil and colleagues. [57]

[^{225} Ac]Ac-PSMA does not pose a significant radiation burden to those in contact with the patient. Therefore, the decision to treat as an inpatient or outpatient should be based on the national regulations on the safe handling of unsealed radioactive sources. If these permit, the patient may be treated as an outpatient.

[^{225} Ac]Ac-PSMA is generally administered as a slow intravenous bolus over 20 to 30 seconds.

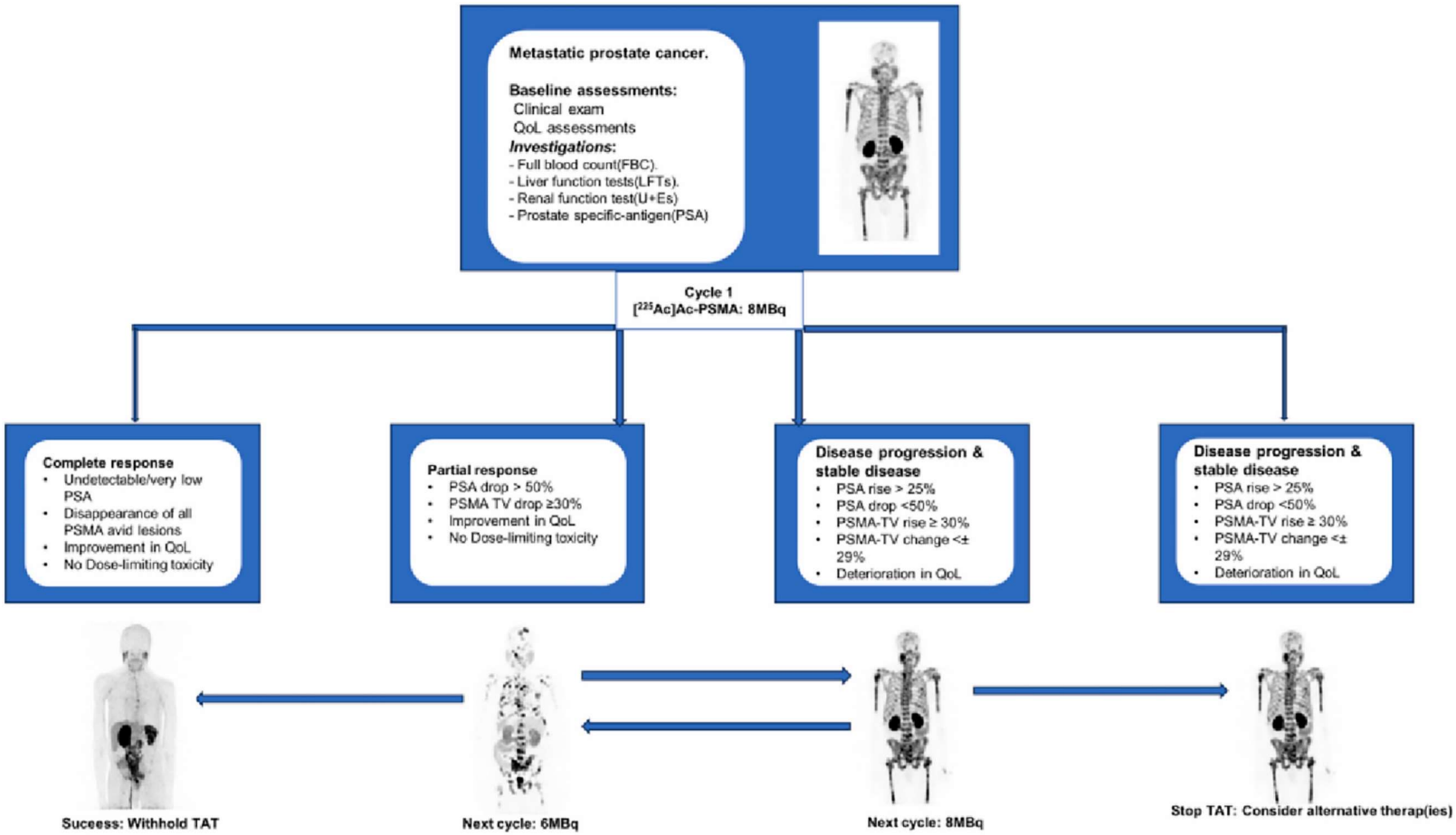

Fig. 1. This shows an example of dose-escalation and de-escalation with [^{225}Ac]Ac-PSMA. The patient is initially treated with 8 MBq of [^{225}Ac]Ac-PSMA. If the patient has a partial response as per the EANM/RECIP criteria, the administered activity for the subsequent cycle will be 6 MBq. If they have complete response after 6 MBq (cumulative 14 MBq), [^{225}Ac]Ac-PSMA is deemed successful and stopped. Should the patient have stable disease or disease progression, the activity of [^{225}Ac]Ac-PSMA is maintained at 8 MBq for the next cycle. If no objective response is seen thereafter, [^{225}Ac]Ac-PSMA therapy is rendered unsuccessful and other therapies are considered. QoL: Quality of life; PSMA-TV: Prostate-specific membrane antigen-tumor volume; TAT: targeted alpha therapy.

The patients are encouraged to stay well hydrated and practice good toilet hygiene. This is especially important when it comes to voiding since unbound [225Ac]Ac-PSMA is excreted via urine.

Follow-up and response assessment

In our center, we administer a minimum of 2 cycles. The maximum number of cycles is determined by the patient's response and side-effect profile. Generally, treatment is repeated every 8 weeks. This was based on the early studies with [^{225} Ac]Ac-PSMA-617 by Kratochwil and colleagues who noted that if [^{225} Ac]Ac-PSMA-617 is given every 8 weeks, there is a reasonable trade-off between toxicity and biochemical response.[56] Another factor that influences the dosing frequency is the supply of [^{225} Ac]Ac. The response assessment is assessed in 3 domains: clinical response, biochemical response, and radiological response. This should be ideally done at most 2 weeks prior to therapy.

Clinical response entails the assessment of disease-related or treatment-related symptomatology. This is either by clinical history or using validated semiquantitative quality of life (QoL) assessment tools. These are robust tools that can assess QoL related to both disease and treatment objectively. They include validated questionnaires such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ), Patient-Reported Outcomes Measurement Information System, and Brief Pain Inventory.[58,59,60]

Baseline blood tests (serum PSA; serum urea, electrolytes and creatinine levels, creatinine clearance for eGFR, and LFTs) should be performed as required during follow-up for safety and efficacy assessments. PSA is used for response assessment based on the prostate cancer working group (PCWG) 3 recommendations. [61]

i. PSA response: PSA decline 50% or greater from baseline measured twice 3 to 4 weeks apart.

ii. PSA progression: rise in PSA by 25% from the nadir and an increase of at least 2 ng/mL.

iii. Stable PSA: decline less than 50% or rise less than 25%.

Response Evaluation Criteria in Solid Tumors 1.1 criteria is used to evaluate response to therapy. Although one would think PSMA-PET/CT imaging would be the most appropriate response assessment study, it should be taken into consideration that the downregulation of PSMA expression may be a mechanism of therapeutic resistance. Therefore, other parameters that include the clinical and biochemical response should be considered when using PSMA imaging as a response assessment tool. Reliance on imaging findings on PSMA imaging alone may lead to failure to confirm disease progression when lesions downregulate their expression of PSMA. Nonetheless various groups have demonstrated and endorsed PSMA-PET imaging as a potential tool for response assessment.[62,63,64]

Current evidence for the efficacy of [^{225} Ac]Ac-prostate-specific membrane antigen therapy in metastatic castrate-resistant prostate cancer

Most of the published data on the clinical application of [^{225} Ac]Ac-PSMA have been retrospective in nature due to its use compassionate basis. The Heidelberg group provided the first preliminary insights into the potential of [^{225} Ac]Ac-PSMA TAT for mCRPC. This included its safety and efficacy in the setting of diffuse red marrow metastases, its efficacy in cases resistant to [^{177} Lu]Lu-PSMA, its ability to eradicate high-volume metastases, and its efficacy as a last-line therapy in patients who had multiple conventional therapies for mCRPC.[56] Their cohort consisted of 2 patients (A and B), both with disease progression on conventional therapies. Whereas the next regimen available would have been [^{177} Lu]Lu-PSMA-617, it was contraindicated in patient A since they had diffuse bone marrow involvement. Patient B who had peritoneal carcinomatosis and liver metastases demonstrated progression on [^{177} Lu]Lu-PSMA therapy. They were then considered for [^{225} Ac]Ac-PSMA, which is known for distinct and favorable physical properties compared to β-emitting [^{177} Lu]Lu-PSMA therapy. After 3 cycles of therapy, they demonstrated clinical, biochemical, and imaging response to therapy. The PSA was undetectable and no PSMA-avid lesions were seen on [^{68} Ga] Ga-PSMA-11 PET imaging. [45]

Their follow-up dose-escalation study to define the optimum activity required to achieve the maximum antitumor effect and the dose-limiting organs paved the way for the current global clinical practice on [^{225} Ac]Ac-PSMA therapy. Their approach was estimating the dosimetry using time–activity curves derived from serially obtained [^{177} Lu]Lu-PSMA-617 scans extrapolated to the physical half-life of [^{225} Ac]Ac, assuming instant decay of unstable daughter nuclides. They treated 14 patients with an escalating activity of [^{225} Ac]Ac-PSMA-617, from 50 to 200 kBq/kg body weight, and 100 kBq/kg was determined as the maximum tolerable activity and xerostomia as the dose-limiting toxicity. Notably, xerostomia was the commonest side effect at activity of 100 kBq/kg and above.[56]

The same group proceeded to evaluate the antitumor effect and the duration of disease control of [^{225} Ac]Ac-PSMA in patients treated with first-line, second-line, third-line, and fourth-line regimens using a Swimmer plot as recommended by the PCWG 3.[65] In a cohort of 31 patients treated with 3 cycles of [^{225} Ac]Ac-PSMA, PSA decline 50% or greater was observed in 24 out of 38 (63%) and any PSA response in 33 out of 38 (87%) of patients. The median duration of tumor control was 9.0 months and more importantly, 5 patients demonstrated an enduring response beyond 2 years. This compared favorably with the duration of tumor control seen with other therapies. The duration of disease control regardless of the agent used as first-line, second-line, third-line, or fourth-line agent was 8.0, 7.0, 6.0, and 4.0, respectively. In their study, the commonest first-line, second-line, third-line, and fourth line agents were abiraterone, docetaxel, enzalutamide, and cabazitaxel. The median duration of tumor control was abiraterone (median duration 10.0 months), docetaxel (6.5 months), enzalutamide (6.5 months), and cabazitaxel (6.0 months). In cases where [^{223} Ra]$RaCl_2$ was used, the median duration of tumor control was 4 months. This study provided insights into the antitumor activity of [^{225} Ac]Ac-PSMA in patients who had exhausted other forms of therapy. Furthermore, the study provided evidence of the potential of [^{225} Ac]Ac-PSMA to provide better survival outcomes relative to existing conventional therapies regardless of the stage of disease when it is instituted.[65]

In a cohort of 73 patients (mean age, 69 years; range, 45–85 years), treated with 210 cycles of [^{225} Ac]Ac-PSMA (median treatment cycle = 3, range = 1–8), Sathekge and colleagues demonstrated PSA decline of greater than or equal to 50% in 70% of patients; and any PSA decline in 82%. In 29% of patients, all lesions demonstrated complete resolution on PSMA-PET. The progression-free survival (PFS) and overall survival (OS) were 15.2 months (95% confidence interval [CI], 13.1–17.4) and 18 months (95% CI: 16.2–19.9), respectively. To date, this is the largest series, demonstrating the efficacy, durability of disease control, and survival inducible by [^{225} Ac]Ac-PSMA-617 therapy for mCRPC.[66]

In a much smaller but impactful series, Yadav and colleagues demonstrated median PFS and OS of 12 months (95% CI: 9–13 months) and 17 months (95% CI: 16 months—upper limit not reached), respectively.[67] The PSA response rates were much lower than that of the Pretoria group with 78.6% of the patients achieving any PSA decline, while 39% of patients achieved a PSA decline of 50% or more. This was the first study to provide insights into the effect of [^{225} Ac]Ac-PSMA on the QoL. QoL was accessed using the visual analog score, analgesic score, Eastern Cooperative Oncology Group performance status, and Karnofsky performance status. Statistically significant improvement was noted using these scoring tools, corresponding to improvement in pain severity, need for analgesia, and carrying out activities of daily living.[67]

Two other groups demonstrated comparable quality-of-life effects in patients with mCRPC. Satapathy and colleagues focused on the Health-Related Quality-of-Life Outcomes related to [^{225} Ac]Ac-PSMA in 11 heavily pretreated patients. Pretherapy and posttherapy NCCN-FACT-FPSI-17 questionnaires revealed statistically significant improvement in the total FPSI score (P = .003) as well as the disease-related symptoms-physical (P = .004) and disease-related symptoms-emotional (P = .046) subscores. Significant improvement was noted with respect to pain, difficulty in urination, bone pain, fatigue, and restriction in physical activity.[68] The findings were comparable to those of the Heidelberg group whose patients experienced clinically relevant decrease in pain and QoL improvement in physical and role functioning domains. This group used the EORTC-QLQ-30 and BM-22 questionnaires with a corresponding reduction in the need for analgesia noted.[69]

Multiple other retrospective studies showed an excellent response in patients with visceral metastases and exceptional disease control rates of remission as long as 5 years. Maserumule and colleagues reported an exceptional response in a patient with diffuse lung metastases. The same group also reported an exceptional response of cerebral metastases and widespread skeletal metastases. More importantly, this patient demonstrated a remarkable functional response (resolution of cerebral and extensive skeletal metastases) and biochemical response (decrease in serum PSA level from 788.63 to 6.52 µg/L) after 1 cycle of [^{225} Ac] Ac-PSMA. [70,71,72]

Efficacy of [^{225} Ac]Ac-prostate-specific membrane antigen in the post–[^{177} Lu]Lu-prostate-specific membrane antigen therapy setting

[^{177} Lu]Lu-PSMA has undergone extensive evaluation prospectively and retrospectively. It has demonstrated good antitumor and survival outcomes in patients who have exhausted other conventional therapies.[73,74] In a phase II trial, Hoffman and colleagues a PSA decline of 50% or more was achieved in 17 (57%) patients (95% CI: 37–75). 21 (70%) patients (95% CI: 51–85)

achieved a PSA decline of at least 30%, 13 (43%) patients (20–56) of at least 80% and 6 (20%) patients (8–39) of 96% or higher.[53] On the other hand, the recent phase 3 multicenter VISION trial, which resulted in the FDA approval of [^{177} Lu]lu-PSMA-617 in mCRPC, only 9% had a complete response to therapy, whereas only 41% of patients in the [^{177} Lu]Lu-PSMA-617 cohort had partial response to therapy.[3] These studies demonstrated that despite the good tumor control seen with [^{177} Lu]Lu-PSMA, a large number of patients may not respond to [^{177} Lu]Lu-PSMA and of those who respond, many will experience disease progression. This necessitates the need for a more effective next-line or alternative therapeutic regimen. Authors have used [^{225} Ac]Ac-PSMA therapy with the premise that its physical properties confer superior radiobiological effectiveness that overcomes resistance to [^{177} Lu]Lu-PSMA. Kratochwil and colleagues were the first to demonstrate complete biochemical and imaging response to [^{225} Ac] Ac-PSMA in a patient who had progressed on [^{177} Lu]Lu-PSMA.[45]

A notable study showed a substantial antitumor effect of [^{225} Ac]Ac-PSMA in patients refractory to [^{177} Lu]Lu-PSMA. Any PSA decline and a PSA decline of 50% or greater were observed in 23 (95% CI: 70%–97%) and 17 (95% CI: 46%–81%) of 26 patients, respectively. Higher functional status (ECOG 1/2) was associated with a better prognosis. Liver metastases at initial presentation were associated with shorter PSA-PFS (1.9 vs 4.0 months; P = .02, hazard ratio [HR] 3.01, 95% CI: 0.7 to 13.1), shorter clinical PFS (1.8 vs 5.2 months; P = .001, HR 4.38, 95% CI), and shorter OS (4.3 vs 10.4 months; P = .01, HR 9.35, 95% CI: 1.5–56.9). [76] Compared to other studies, the frequency of a PSA response and the duration of the response were, however, lower than in previous reports for [^{225} Ac]Ac-PSMA- 617 seen in less advanced and patients who were either both chemo and/or [^{177} Lu]Lu-PSMA-naïve. Another important issue was that there were no measurable changes in the global health status/QoL using the EORTC-QLQ30 questionnaire.[65,75,76]

Although a substantial antitumor effect has been demonstrated, the survival is shorter after [^{225} Ac]Ac-PSMA-617 in patients who have received [^{177} Lu]Lu-PSMA compared to those who have not received ^{177} Lu]Lu-PSMA prior to [^{225} Ac]Ac-PSMA-617. Sathekge and colleagues showed that patients with a prior history of [^{177} Lu]Lu-PSMA therapy had a significantly shorter PFS (5.1 months, 95% CI: 3.8–6.5 months vs 16.5 months, 95% CI: 14.3–18.7 months) compared with [^{177} Lu]-PSMA therapy-naïve patients. On multivariate analysis, prior [^{177} Lu]Lu-PSMA therapy was significantly associated with shorter PFS.[66] Comparable results were in a case series of 19 patients with mCRPC who were refractory to treatment with [^{177} Lu]Lu-PSMA (2–9 cycles) by Alan-Selcuk and colleagues. One cycle of [^{225} Ac]Ac-PSMA resulted in a decrease in PSA of more than 50% in 5 of 19 patients (26%). Any decrease in PSA was observed in 11 of 19 patients (58%). Median PFS and median OS were quite low at 3.1 and 7.7 months, respectively. In the Munich series of patients post [^{177} Lu]Lu-PSMA therapy,[75] the median PSA-PFS, clinical PFS, and OS periods were 3.5 (95% CI: 1.8 to 11.2), 4.1 (95% CI: 3–14.8), and 7.7 (95% CI: 4.5–12.1) months, respectively.[75] These good PSA responses with shorter survival rates may have been due to the heterogeneous nature of these populations. Two approaches may be valuable to address this which include randomized control trials to determine which patients are likely to benefit from either therapy. One such study is the currently active phase 1 AcTion trial [clinicaltrials.gov . NCT04597411], which is investigating [^{225} Ac]Ac-PSMA in patients previously treated with [^{177} Lu]-PSMA-I&T or [^{177} Lu]Lu-PSMA-617 radioligand therapy.

Another approach that has been explored in patients refractory to [^{177} Lu]Lu-PSMA therapy has been the use of tandem therapy. This involves using a cocktail of both [^{177} Lu]Lu-PSMA and [^{225} Ac]Ac-PSMA in patients who demonstrate poor response to [^{177} Lu]Lu-PSMA. The Homburg group in a cohort of 20 patients administered [^{225} Ac]Ac-PSMA-617 and then [^{177} Lu]Lu-PSMA-617 in the same week, typically on consecutive days. The median (ranges) of administered activities were 5.3 (1.5–7.9) MBq for [^{225} Ac]Ac-PSMA-617 and 6.9 (5.0–11.6)GBq for [^{177} Lu]Lu-PSMA-617.[78] Their study showed better PSA responses with 13 out of 20 patients (65%) having PSA decline 50% or greater. Comparable response rates were seen in both patients who showed an earlier response to prior [^{177} Lu]Lu-PSMA-617 therapy before developing resistance (n = 12) versus those patients who never responded to the prior [^{177} Lu]-PSMA-617 therapy.[78] Other studies have shown similar results including molecular imaging response based on PSMA-PET imaging.[79] Generally, these studies highlight the antitumor activity of [^{225} Ac]Ac-PSMA against 2 patterns of radio resistant to β-emitting radionuclide therapy for mCRPC, which are acquired and inherent resistance.

[^{225} Ac]Ac-prostate-specific membrane antigen: in the prechemotherapy and/or postandrogen deprivation therapy settings

Radioligand therapies have generally been considered and used at the end of the disease spectrum.[80,81] However, more favorable outcomes and responses to therapeutic regimes are noted in earlier phases of prostate cancer pathogenesis. This may be multifactorial with a predominance of less resistance mechanisms in the earlier phases. To the best of our knowledge, no randomized control trial studies have been published to determine the therapeutic effectiveness as a determinate of the order of therapy after androgen deprivation therapy (ADT) has failed. Better PSA responses have been seen if [^{177} Lu]Lu-PSMA was used in chemotherapy-naive patients.[82] Translation of this to [^{225} Ac]Ac-PSMA is important especially in patients with contraindications to chemotherapy or who may not wish to have chemotherapy at all. Sathekge and colleagues reported on a group of 17 men who had mCRPC therapies other than chemotherapy but inclusive of [^{177} Lu]Lu-PSMA.[57] Sixteen patients demonstrated good antitumor activity of [^{225} Ac]Ac-PSMA-PSMA assessed by serum PSA level and [^{68} Ga]Ga-PSMA-PET/CT. In 14 out of 17 patients, PSA decline 90% or greater was seen after treatment, including 7 patients with undetectable serum PSA following 2 (2 out of 7) or 3 cycles (5 out of 7) cycles of [^{225} Ac]-PSMA-617. Fifteen of 17 patients had a greater than 50% decline in lesion avidity for tracer on [^{68} Ga]Ga-PSMA-PET/CT including 11 patients with complete resolution (PET-negative and either stable sclerosis on CT for bone or resolution of lymph node metastases) of all metastatic lesions.[57] The same group also did a subgroup analysis of treatment outcome and survival in patients who progressed only on ADT. [76] Forty-eight patients (91%) had a PSA decline of at least 50%, and 51 patients (96%) had any decline in PSA. [^{68} Ga]Ga-PSMA-PET findings became negative in 30 patients. The median estimated OS was 9 months for patients with a PSA decline of less than 50% but was not yet reached at the latest follow-up (55 months) for patients with a PSA decline of 50% or more. The estimated median PFS was 22 months for patients with a PSA decline of at least 50% and 4 months for patients with a PSA decline of less than 50%.[76] These studies are congruent with the outcomes seen when [^{177} Lu]Lu-PSMA was applied earlier.[82] This implies that [^{225} Ac]Ac-PSMA may need to be considered in the earlier phases of disease, to harness its full potential. Despite the application of [^{225} Ac]Ac-PSMA as the last line, the median duration of tumor control was 9.0 months. This was excellent compared to earlier applied therapeutic regimens

of abiraterone, docetaxel, enzalutamide, cabazitaxel, and [^{223} Ra]RaCl $_2$ with median durations of tumor control of 10.0, 6.5, 6.5, 6.0 and 4.0 months, respectively.[65] However, the performance of a prospective large multicenter randomized study comparing [^{225} Ac] Ac-PSMA with current standard-of-care treatment options such as enzalutamide, abiraterone acetate, and docetaxel after ADT in different stages of disease is needed.

[^{225} Ac]Ac-prostate-specific membrane antigen: application in the hormone-sensitive setting

In patients with high-volume disease at initial presentation who are presumably hormone-sensitive, various treatment regimens as monotherapy or in combination are recommended by various treatment guidelines. These include ADT, taxane-based chemotherapy, and novel antiandrogen drugs. Some patients may not be able to tolerate these regimens based on their physical status or preferences. They are thus started on ADT alone, which may be insufficient without systemic therapy.[80] This stimulates the need for other tolerable therapies such as [^{225} Ac]Ac-PSMA. Sathekge and colleagues reported a retrospective series of 21 men with untreated bone and visceral metastatic hormone-sensitive prostate carcinoma who refused standard treatment options and were treated with [^{225} Ac]Ac-PSMA-617. [83] The treatment was well tolerated with only grade 1 and 2 xerostomia in 94% of patients. Ninety-five percent of the patients had any decline in PSA and 86% presented with a PSA decline of at least 50% including 4 patients in whom PSA became undetectable. A lower percentage decrease in PSA following treatment was associated with an increased mortality and shorter PFS.[83]

Side-effect Profile of [^{225} Ac]Ac-prostate-specific Membrane Antigen

Ma and colleagues reported on the side-effect profile of [^{225} Ac]Ac-PSMA therapy. Salivary gland toxicity was the most common with any grade occurring in approximately 77.1% and grade 3 or higher salivary gland toxicity occurring in 3%. Anemia was the second commonest toxicity, with any grade occurring in 30.3%, and grade 3 accounting for 7.5% of patients; grade III leukopenia and thrombocytopenia were 4.5% and 5.5%, respectively. Grade 3 nephrotoxicity occurred in 6%. [84]

The most common toxicities observed make sense given that organs expressing significant PSMA expression include salivary glands, lacrimal glands, enterocytes of the small bowel, and the epithelial lining of the proximal convoluted tubules.[85] Further early dosimetry data on TAT showed that salivary glands received the highest radiation dose and are the dose-limiting organ for TAT.[75,85,86] These treatment-related side effects with TAT are also due to both direct and indirect radiation effects (ROS). The salivary gland secretions provide a good milieu for the generation of ROS, making them one of the most radiosensitive organs.[87] The signs and symptoms of salivary gland toxicity include a burning sensation in the mouth, dysgeusia, problems with speech, sleep and mastication, and dental infections. These can adversely affect the patient's QoL.[88,89]

Various groups have aimed to mitigate for salivary gland toxicity. Lessons learnt from head and neck external beam radiotherapy suggest that the general approach should entail reducing radioligand uptake in the salivary glands, administration of radioprotectors, stimulation of salivary gland secretion, and restoration of salivary gland function.[90]

External salivary gland cooling has been explored as a way of reducing radioligand uptake. However, limited benefit was noted with this strategy, no difference in PSMA uptake was seen on PET imaging between the cooled and uncooled salivary glands. [91,92] The administration of botulinum toxin, other anticholinergic drugs, local anesthetics such as lidocaine, and modifications of tracer administration have also shown promise.[57,93]

Sathekge and colleagues[57] exploited the tumor sink effect, that is, decreased uptake in dose-limiting organs in the setting of high tumor burden,[94] to modify the activity of tracer administered through the course of treatment in an effort to reduce the incidence and severity of treatment-induced xerostomia.[57,96] Initial activity of 8 MBq was given, with subsequent de-escalation to 7 MBq, 6 MBq, or 4 MBq for subsequent therapy sessions in patients with good titrated against residual tumor burden. In patients with disease progression, the activity administered was increased against the tumor burden. Reduced toxicity in the salivary glands was observed with only grade 1/2 xerostomia seen in all patients, and no xerostomia severe enough to lead to treatment discontinuation. Importantly, the antitumor effect and long-term outcomes were maintained despite the dose modifications in subsequent cycles.[57]

Other groups have evaluated the tandem administration of [^{225} Ac]Ac-PSMA and [^{177} Lu]Lu-PSMA. Khreish and colleagues were the first to report their experience with 1 course of [^{225} Ac]Ac-PSMA-617/[^{177} Lu]Lu-PSMA-617 tandem therapy in 20 patients with mCRPC[78]. They reported grade 1 (very mild), and grade 2 (mild) xerostomia in 8 out of 20 patients (40%) and 5 out of 20 (25%). No grade 3/4 xerostomia was reported, and no patient stopped therapy due to dryness of the mouth. This included patients with previous [^{177} Lu]Lu-PSMA therapy.[78] Lower incidences of grade 1/2 I/II xerostomia were also reported in follow-up studies that used tandem therapy.[79,95]

In a recent retrospective analysis of patients with extensive skeletal metastases, severe hematotoxicity was rare.[96] The study included 106 patients who received a median of 4 cycles of [^{225} Ac]Ac-PSMA-617. Among these 106 patients, 32.1% presented with a super scan pattern on [^{68} Ga]Ga-PSMA-11 PET/CT, the rest had more than 20 skeletal lesions, and 92% had baseline hematological abnormalities. Only 1 patient had grade 4 thrombocytopenia. Grade 3 anemia, leukopenia, and thrombocytopenia were seen in 1 (0.9%), 3 (2.8%), and 2 (1.9%) patients, respectively. Age, number of treatment cycles, and the presence of renal dysfunction were significant risk factors for hematologic toxicity of [^{225} Ac] Ac-PSMA-617 therapy.[96] Comparable results were seen in other groups and a previous meta-analysis.[56,66,97] Satapathy and colleagues noted that clinically significant toxicity was limited with grade 3 or greater xerostomia, anemia, leukopenia, thrombocytopenia, and nephrotoxicity occurring in 1.2%, 12.3%, 8.3%, 6.3%, and 3.8% of the patients, respectively.[97] The rarity of hematological side effects is in line with the shorter path length of α-particles compared with β-particles, which implies that high energy is deposited within the targeted bone metastases with a limited dose delivered to the surrounding red marrow.[11,54]

Chronic kidney disease after [^{225} Ac] Ac-PSMA therapy is rare, but seen. Satapathy and colleagues showed that 3.8% of patients had grade 3 or greater toxicity warranting the stoppage of therapy.[97]

Resistance and Mutations

Genotypical features conferring resistance to TAT point toward an increased prevalence of mutations in the DNA damage repair machinery. P53 protein halts cell cycle progression in response to DNA damage by acting via cyclin and cyclin-dependent kinases. Mutations in the TP53 the gene, which codes for the p53 protein have been demonstrated in patients with poor prognosis to [^{225} Ac]Ac-PSMA.[98] Patients with resistance to PSMA TAT despite PSMA positivity frequently harbor mutations in DNA damage repair and checkpoint genes.[99,100,101] In 7 tumor samples analyzed by Kratochwil and colleagues, deleterious or presumably deleterious mutations affecting *TP53* , *CHEK2* , *ATM* , and *BRCA1* , *BRCA2* , *PALB2* , *MSH2* , *MSH6* , *NBN* , *FANCB* , and *PMS1* were found. [101] Knowledge of these pathogenic germline variants is important for patient selection for TAT and the possible design of combination therapies that will improve outcomes in patients with resistance to TAT. This has opened the door for combination therapy with poly(ADP) ribosyl polymerase inhibitors such as olaparib to be used in combination with radioligand therapy. Olaparib and other PARP inhibitors as either monotherapy or combination therapies have been demonstrated to prolong survival in patients harboring *BRCA1/2* germline mutations.[102,103] The ability of olaparib to potentiate the antitumor effect of [^{177} Lu]Lu-PSMA is currently being evaluated (NCT03874884). This is a possible route that trials on [^{225} Ac]Ac-PSMA will take later. Alpha particles are well known to be associated with abscopal effects as an indirect immune-mediated cytotoxic effect in nontarget cancer cell.[12] This is due to the release of tumor neoantigens that potentiate the host adaptive immune system suggesting a possible role of immunotherapy.[104] However, little success has been achieved with the use of immunotherapy agents in the treatment of mCRPC. This limited success has been attributed to the immunologic coldness of prostate cancer resulting from poor expression of neoantigens.[105]

Rechallenge options

Despite the success of [^{225} Ac]Ac-PSMA, some patients who initially respond to therapy demonstrate disease recurrence. Such patients are likely to have exhausted other therapies and [^{225} Ac]Ac-PSMA becomes the only option. The initial response of the patient to therapy should be part of the qualifying criteria. Therapy should only be administered in patients who demonstrated an initial objective response. The toxicity from past cycles of [^{225} Ac]Ac-PSMA should also be considered. In addition, the clinical status of the patient should be considered, and such rechallenge be considered in patients who demonstrate a good functional status and prognosis. Figs. 2 and 3 demonstrate a patient with an initially excellent response to therapy, followed by more than 24 month remission. Rechallenge with [^{225} Ac]Ac-PSMA-617 shows more than 90% PSA decline.[106]

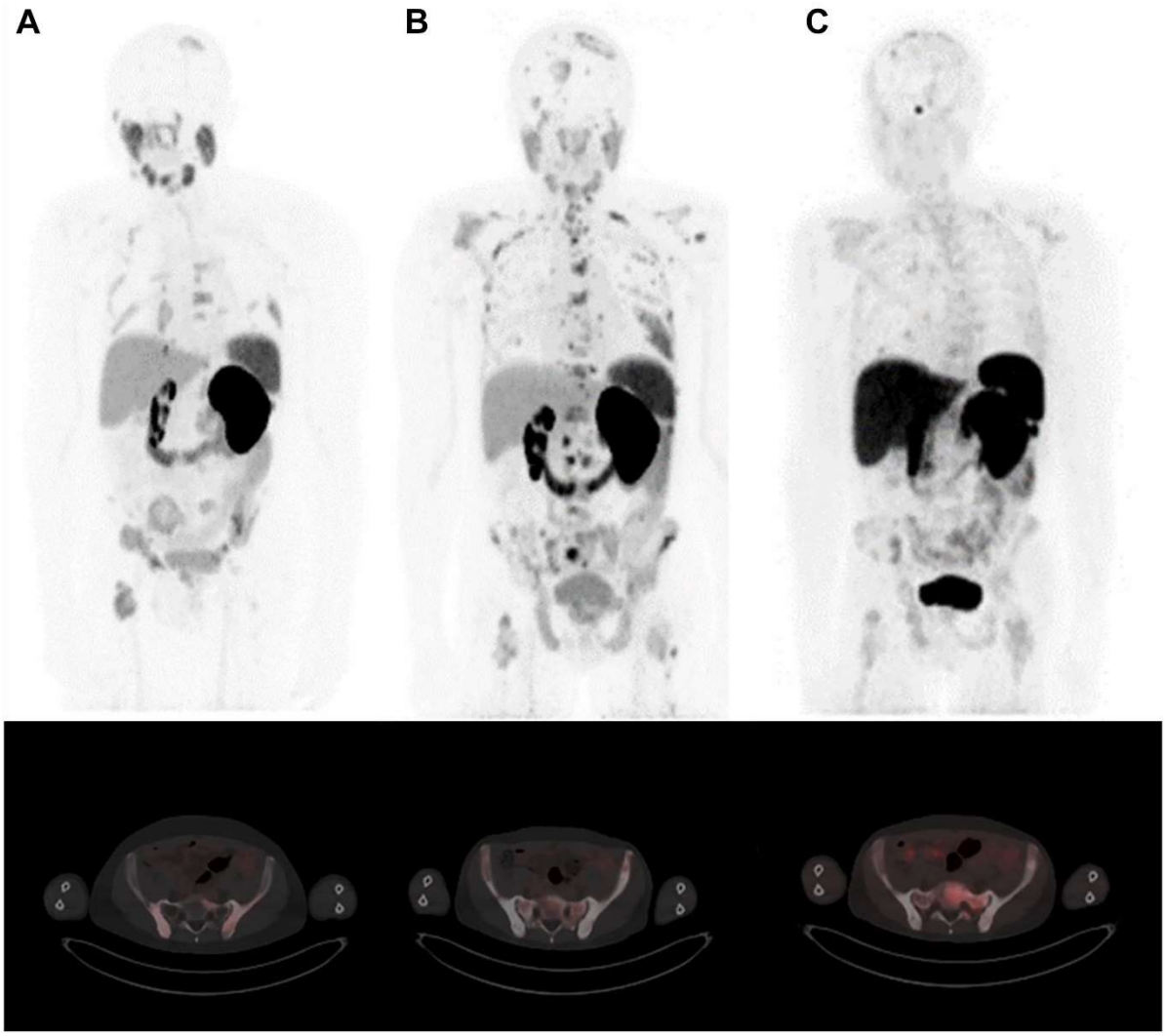

Fig. 2. A case of a 55 year old male patient with metastatic prostate cancer stage IVb, Gleason 5 + 4 diagnosed in February 2021. *Panel A (MIP)* is a [^{68} Ga]Ga-PSMA-11 PET/CT done after androgen deprivation therapy and chemotherapy, which demonstrated PSMA-avid metastatic bone disease. *Panel B (MIP)* demonstrates progression after 5 cycles of [^{225} Ac]Ac-PSMA-617; PSA rose from 94 to 294 ng/mL. *Panel C (MIP)* [^{68} Ga]Ga-DOTATATE PET/CT demonstrates tracer avid skeletal metastases, for example, sacral uptake (Panel C axial) demonstrates DOTATATE uptake despite PSMA negativity in [^{68} Ga]Ga-PSMA-PET/CT images. This is a classic case of neuroendocrine dedifferentiation in progressive mCRPC.

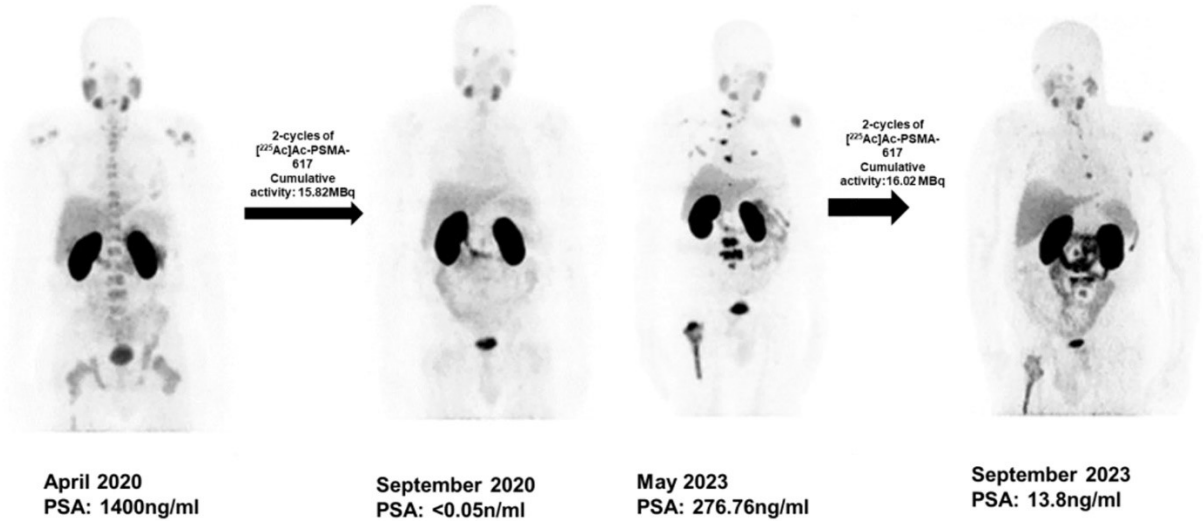

Fig. 3. [^{68} Ga]Ga-PSMA-11 PET/CT images of a 67 year old male patient with mCRPC postchemotherapy demonstrated excellent response to [^{225} Ac]Ac-PSMA-617 at initial presentation. The patient went on remission for more than 24 months. Rechallenge with [^{225} Ac]Ac-PSMA-617 demonstrates more than 90% drop in PSA levels. In addition, resolution of PSMA-avid lesions is noted.

Summary

This review discusses α-PSMA radiopharmaceuticals and their clinical applications worldwide. We introduce the radiopharmaceuticals that have been evaluated in the preclinical setting and discuss the mechanisms that confer increased radiobiological effectiveness. The relative advantages of the different PSMA TAT are also discussed. The discussion then focuses on [^{225} Ac] Ac-PSMA-617, which has been evaluated in multiple clinical retrospective studies. These showed that it can be used in situations where resistance to other therapies exists, it is safe and associated with long-term survival and good tumor control. It is suitable in metastatic hormone-sensitive prostate cancer and in mCRPC after or before the use of novel antiandrogen therapies, chemotherapies, or [^{177} Lu] Lu-PSMA-617. Detailed patient selection criteria, preparation, and administration of TAT is also outlined.

Clinics care points

- Compared to other therapies in mCRPC, TAT with PSMA radiopharmaceutical is associated with a good antitumor effect and prolonged survival outcomes.
- Salivary gland toxicity is the dose-limiting toxicity; however, hematotoxicity and renal toxicity are infrequent.

Disclosure

Ethical approval and consent to participate: Although this is a review article, ethics approval and informed consent for the images used are available. *Competing interests:* The authors declare that they have no competing interests. *Consent for publication:* Informed patient consent for publication of [^{68} Ga] Ga-DOTATATE PET/CT and [^{68} Ga]Ga-PSMA-PET/CT images and other relevant information was obtained. *Availability of data and materials:* The articles quoted and referenced are available online as referenced. The images used for the review are

available from the corresponding author on request. *Funding:* The authors declare that the review was conducted in the absence of any commercial or financial relationships.

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1 Contributed equally.

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