REVIEW

Advances in targeted alpha therapy for prostate cancer

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Amongst therapeutic radiopharmaceuticals, targeted alpha therapy (TαT) can deliver potent and local radiation selectively to cancer cells as well as the tumor microenvironment and thereby control cancer while minimizing toxicity. In this review, we discuss the history, progress, and future potential of TαT in the treatment of prostate cancer, including dosimetry-individualized treatment planning, combinations with small-molecule therapies, and conjugation to molecules directed against antigens expressed by prostate cancer cells, such as prostate-specific membrane antigen (PSMA) or components of the tumor microenvironment. A clinical proof of concept that TαT is efficacious in treating bone-metastatic castration-resistant prostate cancer has been demonstrated by radium-223 via improved overall survival and long-term safety/tolerability in the phase III ALSYMPCA trial. Dosimetry calculation and pharmacokinetic measurements of TαT provide the potential for optimization and individualized treatment planning for a precision medicine-based cancer management paradigm. The ability to combine TαTs with other agents, including chemotherapy, androgen receptor-targeting agents, DNA repair inhibitors, and immuno-oncology agents, is under investigation. Currently, TαTs that specifically target prostate cancer cells expressing PSMA represents a promising therapeutic approach. Both PSMA-targeted actinium-225 and thorium-227 conjugates are under investigation. The described clinical benefit, safety and tolerability of radium-223 and the recent progress in TαT trial development suggest that TαT occupies an important new role in prostate cancer treatment. Ongoing studies with newer dosimetry methods, PSMA targeting, and novel approaches to combination therapies should expand the utility of TαT in prostate cancer treatment.

Key words: targeted alpha therapy (TαT), radium-223, prostate cancer, prostate-specific membrane antigen (PSMA)

Introduction

The therapeutic effectiveness of specific radionuclides is determined by the specificity of targeting and the innate characteristics of the particle emitted, including potential range, effective travel distance in tissue, and the magnitude of energy emitted [1]. Radionuclides may be classified by their emission of particles, including alpha and β particles [2]. Beta particles have a low linear energy transfer (LET) (0.2 keV/μm), which results in sparse ionization events, individual DNA lesions, and repairable single-strand DNA breaks. Alpha particles have higher LET (50–230 keV/μm), which results in clusters of double-strand breaks (DSBs) in DNA and increased cytotoxicity relative to β particles. Alpha particles also have a shorter path length in tissue (50–100 μm) compared with β particles (1000–10 000 μm). The short range of alpha particle radiation has the potential to minimize cytotoxic damage in non-targeted cells, potentially enabling specific cancer cell targeting with reduced toxicity to normal cells [3, 4]. This is exemplified by radium-223 dichloride

(radium-223, Xofigo®), a first-in-class alpha particle–emitting agent approved for castration-resistant prostate cancer (CRPC) with symptomatic bone metastases [5]. Radium-223 is a calcium mimetic that can preferentially bind to areas of hydroxyapatite deposition, such as bone metastases in prostate cancer (PC) [6–8]. Other bone-seeking, β particle-emitting radionuclides, such as strontium-89 and samarium-153-EDTMP, are indicated for pain relief for skeletal metastases [9–11]. Although these radionuclides provided pain palliation in bone-metastatic CRPC (mCRPC), they have failed to confer survival benefit [10, 12]. In contrast, in addition to reducing bone pain in a subset of patients, radium-223 provided survival benefit when added to best standard of care (SoC) [7, 13, 14]. Recent progress in targeted alpha therapy (TαT) offers the potential to deliver cytotoxic radiation in a highly localized manner [3, 4]. In addition to exploring radium-223 in combination with other cytotoxic agents, androgen receptor (AR)-targeting agents, or immuno-oncology agents, preclinical and clinical studies investigating other alpha particle-emitting radionuclides for use as TαTs (e.g. actinium-225 and thorium-227 conjugates) are ongoing (Table 1). This review will discuss the history, progress, and future potential of TαT for the treatment of PC, including (i) treatment optimization and individualized planning; (ii) combination therapies (e.g. radium-223 with AR-targeting agents, cytotoxic agents, or immuno-oncology agents); (iii) prostate-specific membrane antigen (PSMA) as an emerging therapeutic target; and (iv) next-generation TαTs (e.g. targeted thorium-227 and actinium-225 conjugates).

What is the proof of concept for TαT?

Mechanism of action of radium-223, the first-in-class TαT in PC

Radium-223 is the most-investigated TαT in clinical settings. Radium-223 is a calcium mimetic that is recruited to newly forming bone and induces an intense, local cytotoxic effect, affecting both cancer cells and the tumor microenvironment [8]. In murine tumor models, radium-223 suppresses tumor-induced osteoblastic activity, tumor growth, and pathological bone formation [8]. In PC xenograft models, radium-223 inhibits abnormal bone metabolic activity by reducing the number of bone-forming osteoblasts and obliterating bone-degrading osteoclasts [8]. In vitro studies suggest that radium-223 may enhance T-cell-mediated lysis of prostate, breast, and lung carcinoma cells through induction of immunogenic cell death [35, 36].

Clinical outcomes of radium-223 treatment

Radium-223 has provided clinical proof of concept that TαT is an effective treatment strategy for PC [5]. In phase III ALSYMPCA trial [37] of patients with bone-mCRPC and no known visceral metastases, radium-223 significantly extended overall survival (OS) [radium-223, 14.9 months; placebo, 11.3 months; hazard ratio, 0.70 (95% CI 0.58–0.83), $P < 0.001$] [7]. Radium-223 also

Table 1. TαTs in prostate cancer				
TαT	MoA	Half-life	Number of alpha particles emitted	Highlights of ongoing clinical trials or key findings
Radium-223 dichloride	Bone-seeking alpha-emitting radionuclide [8]	11.4 days [15]	4 [15]	The phase III PEACE III trial on the combination of radium-223 and enzalutamide in mCRPC [16] The phase III DORA trial on the combination of radium-223 and docetaxel in mCRPC [17] Phase I trial on the combination of radium-223 and atezolizumab in mCRPC [18]; phase II trials on pembrolizumab [19] or sipuleucel-T [20] and radium-223 in mCRPC Phase Ib trial of radium-223 and niraparib (PARPi) in CRPC [21]; phase I/II trial of radium-223 and olaparib (PARPi) in mCRPC [22]
[213]Bi-PSMA-617	PSMA-targeting small-molecule ligand conjugated with alpha-emitting radionuclide	45.6 minutes [23]	1 [23]	Molecular imaging and biochemical responses in a patient with mCRPC [24]
[225]Ac-PSMA-617		10.0 days [25]	4 [25]	Antitumor activity was observed in patients with mCRPC with xerostomia as dosing-limiting factor and reason of treatment discontinuation [26–28]
[211]At-PSMA-pentanedioic acid		7.2 h [29]	1 [29]	Significant tumor growth delay and improved survival were seen in preclinical prostate cancer xenograft model and mice bearing prostate cancer micrometastases [30]
[227]Th-PSMA-IgG1	PSMA-targeting mAb conjugated with alpha-emitting radionuclide	18.7 days [31]	5 [31]	Preclinical antitumor activity and safety were observed in models of prostate cancer [32, 33]; phase I trial of [227]Th-PSMA immune-conjugate in mCRPC [34]

CRPC, castration-resistant prostate cancer; DSB, double-strand breaks; mAb, monoclonal antibody; mCRPC, metastatic CRPC; MoA, mechanism of action; PARPi, poly (ADP-ribose) polymerase inhibitor; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; TαT, targeted alpha therapy.

Table 2. Summary of potential biomarkers for treatment response with radium-223

Potential biomarker	Rationale	Clinical evidence
Alkaline phosphatase (ALP)	ALP is a nonspecific marker of osteoblast activity [40]	Patients treated with radium-223 experienced significantly prolonged time to increase in tALP and a greater tALP response compared with placebo [7]
		tALP decline at 12 weeks after radium-223 was initiated correlated with longer OS, but did not meet statistical surrogacy requirements [41]
Lactate dehydrogenase (LDH)	LDH is a metabolic enzyme that participates in the glycolysis and gluconeogenesis pathways, important for tumor growth [42, 43]	LDH decline at 12 weeks after radium-223 was initiated correlated with longer OS, but did not meet statistical surrogacy requirements [41]
		Increased levels of LDH are associated with poor clinical outcomes in prostate cancer and aggressive phenotypes in patients with bone metastases [43]
CHEK2 (DNA repair gene)	Radium-223 emits alpha particles, which have high LET, resulting in clusters of DSBs in DNA. Therefore, patients with mCRPC with alterations in their DNA repair pathway genes may be particularly susceptible to radium-223 treatment [44–46]	Mutation corresponds to a higher risk of prostate cancer, but there is no clear familiar association [47]
		More than one patient who responded to radium-223 was found to have a mutation in this gene [44, 45]
BRCA2 (DNA repair gene)		Mutation corresponds to a higher risk of prostate cancer, with a familiar association [48]
		More than one patient who responded to radium-223 was found to have a mutation in this gene [44, 46]
MRE11A (DNA repair gene)		A patient who responded to radium-223 was found to have a mutation in this gene [44]
CHD1 (DNA repair gene)		Loss of CHD1 in prostate cancer results in increased sensitivity to DNA damaging agents [49]
		A patient who responded to radium-223 was found to have a mutation in this gene [44]
SPOP (DNA repair gene)		The most commonly mutated gene in primary prostate cancer that serves to modulate DNA DSB repair [50]
		A patient who responded to radium-223 was found to have a mutation in this gene [44]

tALP, total alkaline phosphate; OS, overall survival; CRPC, castration-resistant prostate cancer; mCRPC, metastatic CRPC; LET, light energy transfer; DSB, double-strand break.

provided clinically meaningful improvement in health-related quality of life (QoL) and prolonged the time to first symptomatic skeletal event (SSE) and subsequent SSEs [7, 13].

Despite these results, median times to increase in prostate-specific antigen (PSA) levels were similar among treatment arms [7]. While rising PSA has been used as a biomarker for increased tumor growth, it has not been proven to be a reliable biomarker for therapies that do not directly affect the AR pathway [38, 39]. Potential biomarkers for treatment response with radium-223, including alkaline phosphatase (ALP) and lactate dehydrogenase (LDH), are summarized in Table 2. Mutations in DNA repair pathway genes are included, as patients with these alterations may be particularly susceptible to radium-223 treatment [44–46].

Combining radium-223 with second-generation AR-targeted therapies

Radium-223 has 6 years of real-world evidence supporting its efficacy and safety in mCRPC [7, 13, 14]. Because abiraterone and enzalutamide have both been shown to improve progression-free survival and OS as a first-line treatment of mCRPC, and neither has overlapping toxicity with radium-223, the combinations of these agents with radium-223 are being investigated [51, 52]. In a retrospective analysis of an international, early access, open-label, single-arm, non-randomized trial including 696 patients with mCRPC, radium-223 used with initial and concurrent treatment with abiraterone or enzalutamide improved survival with no unexpected safety concerns [53]. In the eRADicAte study (NCT02097303), an investigator-initiated, phase II, prospective, single-arm study including 31 patients with mCRPC, radium-223 in combination with abiraterone plus prednisone (initiated <90 days before or <30 days after the first radium-223 treatment) conferred clinically meaningful improvements in QoL and pain, without unexpected adverse toxicities [54]. However, the phase III ERA 223 trial (NCT02043678) investigating radium-223 in concurrent combination with abiraterone plus prednisone/prednisolone raised safety concerns: more fractures (28.6% versus 11.4%, based on central radiological review) were observed in the combination arm versus the arm with abiraterone plus prednisone/prednisolone alone [55, 56]. It should be noted

that 79% of the fractures in the combination arm were not at sites of bone metastasis and osteoporotic fractures were most common [57]. The fact that the combination therapy in ERA 223 was administered concomitantly may partially explain the difference in safety profile compared with the ALSYMPCA, eRADicAte, and REASSURE studies. If the combination therapy was instead sequential, this may have allowed the bone to recover from the impact of the normal hormonal agent, thus preventing radium-223 from having a further compounding effect on bone irradiation. Additional analysis of the ERA 223 data showed a lower fracture rate in both study arms in patients who received bone health agents (BHAs) than in those who did not [57], suggesting that the use of BHAs could mitigate the risk of bone fractures for all patients.

The US Food and Drug Administration evaluated the data of ERA 223 and added a warning statement on the use of radium-223 in combination with abiraterone acetate plus prednisone/prednisolone [5]. The Japanese Pharmaceuticals and Medical Devices Agency and Health Canada also issued a similar precaution [58, 59]. However, the European Medicines Agency (EMA) restricted the use of radium-223 to patients who have progressed following two prior systemic treatments for bone-mCRPC or who are ineligible for other treatments. The EMA also issued a contraindication for use in combination with abiraterone acetate plus prednisone/prednisolone [60]. Radium-223 is also being studied in combination with enzalutamide in ongoing phase II (NCT02225704) and phase III trials (NCT02194842) [16, 61]. The initial results of the phase III PEACE III (NCT02194842) trial show that, while fractures increased when radium-223 was added to enzalutamide, this risk was nearly abolished with continuous use of BHAs such as zoledronic acid [62]. After the trial was amended to make BHAs mandatory, no excess fractures were observed in the radium-223 arm [62].

Can we personalize treatment and optimize clinical outcomes of TαT through the addition of dosimetry considerations?

Is TαT dosimetry feasible?

One advantage of TαT compared with other systemic advanced PC modalities is that it enables collection of pharmacokinetic data by imaging in a clinical study setting, which can be used for dosimetry calculations [63]. Radiation dosimetry provides a logical basis for understanding the biological effects of radiation quantities and comparing the effects of different radiation-based treatments [64]. Owing to uptake heterogeneity of alpha particle emitters on a small scale and their potent cytotoxicity, macroscopic dosimetry at the tumor and organ levels is insufficient, and thus microdosimetry that takes into consideration the activity distribution as a function of time at the cellular and subcellular levels should be further developed for more-precise dosimetry calculations [64]. Currently, several small-scale modeling and microdosimetric approaches are being developed, with potential application to clinical imaging and dosimetry [63, 65–67].

Quantification of radium-223 uptake

In vivo dosimetry requires in vivo radium-223 uptake quantification. The low gamma-radiation yield generated through the radium-223 decay pathway allows quantitative imaging of radium-223 therapy and individualized biodistribution studies, although long image acquisition times limit the widespread use of this option [68–70].

Recent evidence has demonstrated a potential correlation between absorbed dose and local lesion response to TαT [69]. A study including nine patients with bone metastases reported that the lesion uptake quantification of radium-223 was significantly correlated with that of technetium-99m-methylene diphosphonate [70]. This introduces the possibility of using conventional radiolabeled diphosphonate scintigraphy to contour bone lesions and define lesion extent in a more reliable manner. Overlapping radium-223 images of the region of interest allow for more accurate radium-223 uptake quantifications for dosimetry and for the assessment of local response of bone metastases to the therapy (i.e. lesion geometric extent and uptake) [70].

Dosimetry and clinical outcomes

The feasibility of TαT dosimetry (e.g. in vivo quantification of radium-223 uptake) [70] might introduce the possibility of clinically investigating the value of personalized treatment and the outcome of radium-223 in relation to the absorbed dose. Recently, in a study including five patients with mCRPC, a correlation between fluorine-18-fluoride (^{18}F-fluoride) and radium-223 uptake was observed [69]. This study, to our knowledge, represents the first observed correlation between absorbed dose and local lesion response of TαT, suggesting that quantitative ^{18}F-fluoride imaging might predict radium-223 uptake and, potentially, treatment response. More robust studies using more advanced imaging techniques are needed to confirm these preliminary findings, explore treatment optimization, and investigate the potential of dosimetry to predict clinical outcomes [69, 70].

In overall survival analyses of the number of radium-223 injections in patients with mCRPC in the US expanded access program, OS was longer in patients receiving five or six injections versus those receiving one to four injections [71]. However, a post hoc analysis of the ALSYMPCA trial showed similar findings with five or six injections of placebo versus one to four injections of placebo [72]. Further study is needed to determine the dosimetry of multiple cycles of radium-223 incorporated in the bone, to assess its impact on biological activity and to investigate the potential of radium-223 dosimetry for treatment optimization and individualized treatment plans [68]. A randomized trial (NCT02023697) compared SSE-free survival (SSE-FS) with different radium-223 regimens in 391 patients with mCRPC and bone metastases: standard activity (55 kBq/kg q4w for 6 cycles), high activity (88 kBq/kg q4w for up to 6 cycles), and extended standard activity (55 kBq/kg q4w for up to 12 cycles) [73]. No statistically significant differences in SSE-FS were observed between the standard activity and either the high or extended standard activity. However, an increased incidence of grade ≥3 treatment-emergent AEs were observed in the latter groups. This result supports the approved radium-223 regimen [73] and also

supports the interest of dosimetry calculation to be used to individualize the 'optimal' activity regimen, as increased- or extended-activity regimens may not necessarily improve efficacy.

The possibility of evaluating TαT distributions after injection and predicting absorbed radiation doses and exposure within tumor and normal tissues introduces the potential for optimizing treatment to maximize antitumor effect while sparing normal tissues [63].

What is the future of TαT in PC?

Radium-223-based radioimmunoconjugates were challenging to develop due to the difficulties associated with stable chelation and conjugation of radium-223 to biomolecules [74, 75]. However, combination of radium-223 with other treatments and at earlier disease stages may broaden its clinical utility [76]. For example, combination therapy of radium-223 with other antitumor agents [e.g. chemotherapy, AR-targeting agents, DNA damage response (DDR) inhibitors, and immuno-oncology drugs] for PC may be a viable treatment approach. Clinical trials are ongoing to assess these combinations (Tables 1 and 3). Additionally, certain alpha emitters can be targeted to tumors by conjugating them to small molecules (e.g. actinium-225–PSMA-617 and bismuth-213–PSMA-617) [24, 26, 78] or radioimmunotherapy [e.g. thorium-227 conjugated to a monoclonal antibody (mAb)] that bind to specific antigens (e.g. PSMA) on tumor cells [3, 26]. Many preclinical and clinical studies are ongoing to investigate the potential of these therapeutic options, which may expand the utility of TαT in the management of PC.

How to develop combination therapies which harness the MoA of TαT?

In addition to combining radium-223 with best SoC (e.g. local external-beam radiation therapy, corticosteroids, antiandrogens, estrogens, estramustine, or ketoconazole) [5], chemotherapy

(e.g. docetaxel in the phase III DORA trial [NCT03574571] [17]) and other antiandrogens (e.g. enzalutamide in the phase III PEACE trial [16]), the MoA of radium-223 provides a basis for investigating its potential combination with other therapies, such as immuno-oncology agents and DDR inhibitors.

Combining TαT with immuno-oncology agents

In addition to cytotoxicity caused by the production of difficult-to-repair clusters of DNA DSBs (targeted effects), TαT may also produce off-target effects, such as systemic bystander (abscopal) effects that may be observed at distances from the target [3, 4, 64, 79, 80]. These systemic bystander effects are potentially mediated by the immune response [79] and could be exploited by appropriate treatment combinations. Combining alpha-emitted radiation and immunostimulatory therapies, such as antiprogrammed death receptor-(ligand)1 (PD-1/PD-L1) or anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4) mAbs, has been shown to reduce nonirradiated metastatic tumor size and of metastatic spread [79]. However, randomized trials to confirm these preliminary findings are needed. Radium-223 has also been demonstrated to sensitize breast, prostate, and lung carcinoma cell lines to cytotoxic T-lymphocyte-mediated lysis by the induction of immunogenic cell death [35]. In *in vitro* cancer model systems, radium-223 can increase expression of major histocompatibility complex-I, induce endoplasmic reticulum stress response in tumor cells, and upregulate the expression of calreticulin and induce its surface translocation. These events ultimately augment tumor sensitivity to T-lymphocyte-mediated lysis [35]. The ability of TαT to induce immunogenic modulation and enhance T-cell-mediated tumor cell lysis across multiple human tumor cell lines suggests wide-ranging applicability and a potential for combination with immuno-oncology agents [35], such as atezolizumab [81], pembrolizumab [82], and sipuleucel-T [83]. Given that TαT may modulate tumor phenotype and enhance T-cell lysis, it has been hypothesized that the immunostimulatory environment created by TαT may potentiate the antitumor activity of these immunotherapies [35]. Given the non-overlapping safety profiles of these

Table 3. Clinical trials investigating combination therapies of TαT and immuno-oncology agents or DDR inhibitors

Agents in combination with TαT	Therapeutic indication	Phase	ClinicalTrials.gov identifier
Immuno-oncology agents in combination with radium-223			
Atezolizumab (PD-L1 mAb)	mCRPC with disease progression after androgen pathway inhibitor treatment	I	NCT02814669 [77]
Atezolizumab (PD-L1 mAb)	Urothelial carcinoma with bone metastases and disease progression after platinum-based chemotherapy	I	NCT03208712 [18]
Pembrolizumab (PD-1 receptor mAb)	mCRPC	II	NCT03093428 [19]
Sipuleucel-T (autologous cellular immunotherapy Targeting PAP)	Asymptomatic or minimally symptomatic bone-metastatic CRPC	II	NCT02463799 [20]
DDR inhibitors in combination with radium-223			
Niraparib (PARPi)	Bone-metastatic CRPC	Ib	NCT03076203 [21]
Olaparib (PARPi)	Bone-metastatic CRPC	I/II	NCT03317392 [22]

ATRi, ataxia telangiectasia and Rad3-related protein inhibitor; CRPC, castration-resistant prostate cancer; DDR, DNA damage response; PAP, prostatic acid phosphatase; PARPi, poly(ADP-ribose) polymerase inhibitor; mAb, monoclonal antibody; mCRPC, metastatic CRPC; TαT, targeted alpha therapy.

therapies and their distinctive MoAs from radium-223, it is potentially advantageous to combine TαT and immuno-oncology agents. Currently, phase I trials examining the combination of atezolizumab and radium-223 are ongoing to investigate its potential in treating mCRPC with disease progression after androgen pathway inhibitor treatment (NCT02814669) [77], and in treating urothelial carcinoma with bone metastases and disease progression after platinum-based chemotherapy (NCT03208712) [18] (Table 3). NCT02814669 includes an adaptive study design with a cohort phase to evaluate the safety and tolerability of the combination with concurrent initiation or a staggered dosing (atezolizumab initiated at the beginning of cycle 2 or 3 of radium-223) before a potential randomization phase [77]. Pembrolizumab in combination with radium-223 is under investigation in a phase II trial in mCRPC (NCT03093428) [19]. Sipuleucel-T combined with radium-223 is being investigated in a phase II trial in men with asymptomatic or minimally symptomatic bone-mCRPC (NCT02463799) [20] (Table 3).

Combining TαT and DDR inhibitors

DDR pathways comprise a network of signaling pathways that maintain genomic stability and cell viability by orchestrating the detection and repair of DNA damage with transient cell cycle arrest [84]. As mentioned above and shown in Table 2, several patients with alterations in DDR pathway genes have been shown to respond to radium-223 treatment [44–46]. Ataxia-telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related protein (ATR) kinases are two master regulators of the DDR signaling pathway. ATM is primarily activated by DSBs, whereas ATR responds to a broad spectrum of DNA damage, including DSBs, lesions from interference with DNA replication, and elevated oncogene-induced replication stress [85, 86]. Poly(ADP-ribose) polymerase (PARP) also plays a vital role in DDR and can be activated by a wide range of stimuli (e.g. single-strand breaks, DSBs, and unusual DNA conformations) [87]. Defective PARP functions can lead to genomic instability and cell death, providing a basis for investigating PARP inhibitors (PARPis) in anticancer therapies [87]. It has been hypothesized that combining TαT and ATR inhibitors (ATRis) or PARPis may potentiate synthetic lethality and antitumor effects [76].

TαT and DDR inhibitor combination therapy has been explored in different tumor types [88]. For example, another TαT—thorium-227 conjugate targeting mesothelin, a surface glycoprotein overexpressed in multiple cancer types (e.g. pancreatic, ovarian, and lung cancers and mesothelioma) [89]—has demonstrated synergistic antitumor effects when combined with ATRi or PARPi in preclinical cancer models [88, 90]. These synergistic effects [88, 90] suggest that inhibiting DDR pathways may sensitize cancer cells to TαT and warrant clinical investigation. Currently, multiple clinical studies investigating the potential of combining TαT and DDR inhibitors in patients with mCRPC and bone metastases are ongoing, such as the phase Ib trial of radium-223 and the PARPi niraparib (NCT03076203) [21] and the phase I/II trial of radium-223 and olaparib (NCT03317392) [22] (Table 3).

PSMA—an emerging and promising target for PC therapy

PSMA is a type II transmembrane protein that is expressed at low levels in a variety of tissues (e.g. the prostate, brain, small intestine, salivary glands, and kidneys) and is overexpressed in primary and metastatic PC cells [78, 91–94]. Although 5–10% of men with PC do not express PSMA, and PSMA may not be expressed uniformly within the tumor [95, 96], high levels of expression of PSMA are observed across the spectrum of aggressive and poorly differentiated PC [91–94, 97], making PSMA a promising therapeutic target [98]. PSMA targeting allows the creation
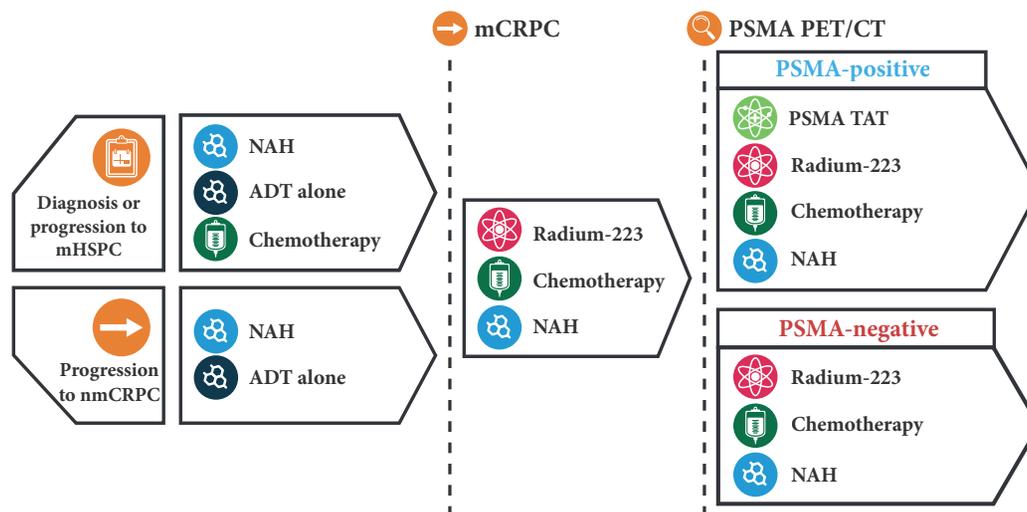

Figure 1. PSMA TαT is complementary to existing therapies for prostate cancer. Depicted is a suggested clinical sequencing, in which PSMA TαTs would be considered after a failure of a first-line therapy for mCRPC and PSMA expression was confirmed positive. ADT, androgen deprivation therapy; CT, computed tomography; mHSPC, metastatic hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; NAH, novel antihormonal; nmCRPC, non-metastatic castration-resistant prostate cancer; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; TAT, targeted alpha therapy.
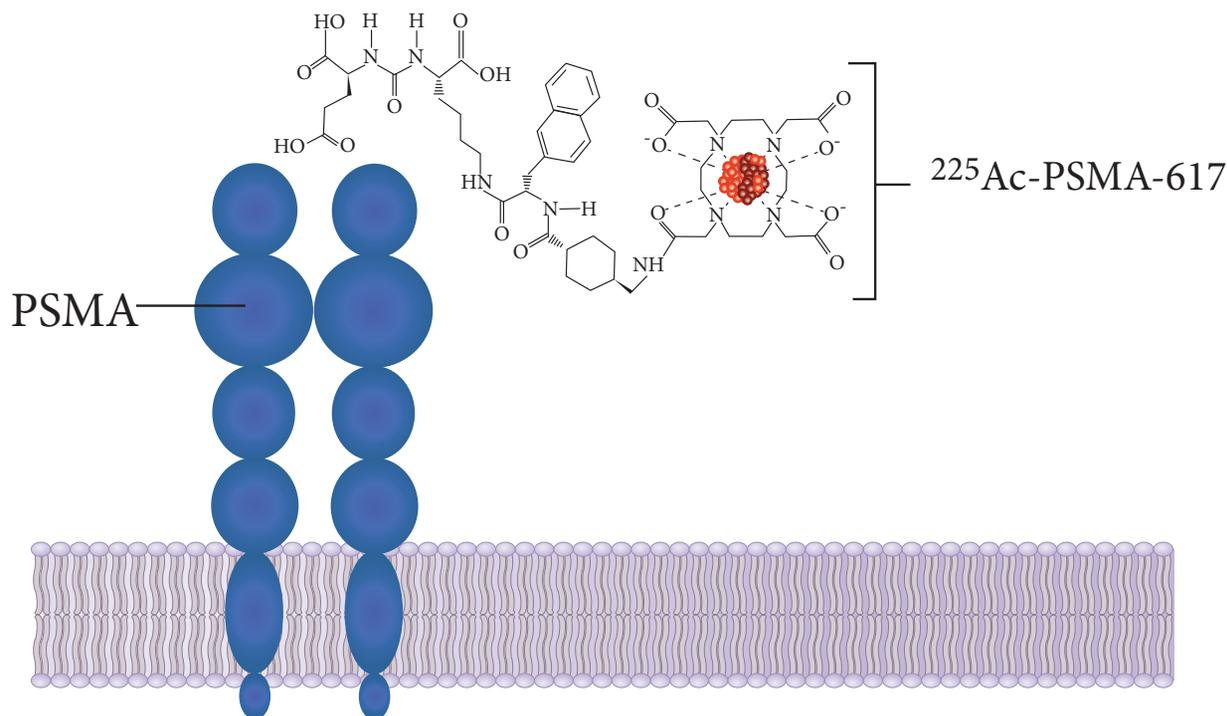
Figure 2. PSMA as a potential therapeutic target for prostate cancer. PSMA is a transmembrane protein overexpressed in prostate cancer. The extracellular domain of PSMA is internalized after ligand binding, allowing intracellular delivery of conjugated therapeutic agents, such as actinium-225. PSMA, prostate-specific membrane antigen.

of novel treatment options that would be complementary to existing therapies [99] (Figure 1).

Investigational agents targeting PSMA can be labeled with different radionuclides, including alpha (e.g. actinium-225 and thorium-227) and β emitters (e.g. lutetium-177 [^{177}Lu] and iodine-131). These agents can be targeted to PSMA via different vehicles, such as antibodies (e.g. thorium-227–labeled anti-PSMA IgG1) and small-molecule ligands (e.g. ^{225}Ac-PSMA-617). While antibodies bind PSMA with high affinity, they have a long serum half-life and greater potential for bone marrow and liver toxicity. Small-molecule ligands have a favorable biodistribution but have risk of off-target toxicity in the kidneys, salivary glands, and lacrimal glands [4, 78, 100]. Other PSMA-targeted therapies under investigation include vaccines and cell therapies.

Among investigational PSMA-targeted therapeutics, β particle-emitting radionuclides targeting PSMA include ^{177}Lu-J591 and ^{177}Lu-PSMA-617. Both agents demonstrated clinical activity in mCRPC [101–108]. A single-arm, single center, phase II study investigating ^{177}Lu-PSMA-617 in mCRPC found that 17 out of 30 patients with mCRPC achieved a ≥50% PSA decline, with a low-toxicity profile and improvement in QoL [101]. A multicenter randomized phase II trial comparing ^{177}Lu-PSMA-617 with cabazitaxel chemotherapy (NCT03392428) is ongoing [109]. The phase III VISION trial investigating PSMA-617 coupled to Lu-177 in mCRPC is also ongoing (NCT03511664) [110]. However, it seems some patients may not respond to ^{177}Lu radioligand therapy, as 9 out of the 30 patients saw no PSA response [111]. Such patients may respond to an alpha particle-emitting radionuclide, such as actinium-225–PSMA-617 (^{225}Ac-PSMA-617) (Figure 2) [26]. Alpha particles are characterized by high LET and

short travel distances; therefore, PSMA-targeted alpha therapies may cause potent and local cytotoxicity to PSMA-expressing cells [3, 4]. Alpha-labeled bisphosphonates, such as ^{225}Ac-EDTMP or ^{225}Ac-zolendronate, may also be considered as they accumulate in the bone microenvironment of osteoblastic lesions [112, 113].

What PSMA–TαT agents are under investigation for PC?

PSMA–TαTs under investigation

Investigational TαTs targeting PSMA include bismuth-213–PSMA-617 (^{213}Bi-PSMA-617) [24], ^{225}Ac-PSMA-617 [95], astatine-211–PSMA–pentanedioic acid (^{211}At-PSMA-pentanedioic acid) [30], and thorium-227-labeled anti-PSMA IgG1 (^{227}Th-PSMA-IgG1) [32]. The first-in-human treatment concept with ^{213}Bi-PSMA-617 was demonstrated in a patient with mCRPC who had progressed on conventional therapy. Molecular imaging (re-staging with ^{68}Ga-PSMA PET/CT) and biochemical (decline in PSA level from 237 to 43 μg/l) responses were observed in this patient after 11 months [24].

Initial clinical experience with targeted actinium conjugates

^{225}Ac-PSMA-617 was investigated in an observational, single-center study as salvage therapy among patients with mCRPC who had exhausted all approved treatment options and had a PSMA-positive tumor phenotype [26]. In the preliminary report

including two patients who received ≥8 prior therapies, [225]Ac-PSMA-617 (100 kBq/kg bimonthly) resulted in a PSA decline below the measurable level and complete imaging response in both cases [26]. In the full report including 14 patients, PSA response was observed in 75% of patients, and promising antitumor activity was detected in brain, bone, liver, and pulmonary lesions. However, persistent xerostomia was regularly reported with a dose of [225]Ac-PSMA-617 ≥100 kBq/kg per treatment cycle and was considered intolerable when the dose exceeded 150 kBq/kg. All-grade hematological AEs occurred in six patients (42.9%), and xerostomia was observed in eight patients (57.1%). With xerostomia being the dose-limiting factor, 100 kBq/kg was considered the maximum tolerable dose. Based on these findings, 100 kBq/kg [225]Ac-PSMA-617 is tolerable and presents promising antitumor activity [27]. Antitumor activity of [225]Ac-PSMA-617 was further demonstrated in 40 patients with mCRPC [28]. Although [225]Ac-PSMA-617 was generally well tolerated, xerostomia remained the main reason for toxicity-associated treatment discontinuation [28]. Clinical trials with larger patient populations are needed to further investigate the efficacy, safety, and patient selection for [225]Ac-PSMA-617.

Preclinical development of targeted astatine and thorium conjugates

[211]At-PSMA-pentanedioic acid has demonstrated significant tumor growth delay in a PC xenograft model. [211]At-PSMA-pentanedioic acid also showed preclinical efficacy by significantly improving survival in mice bearing PC micrometastases. These results expand the potential utility of PSMA–TαTs from macrometastases to micrometastases of PC, including those not visible by traditional imaging techniques [30]. Another PSMA–TαT under preclinical investigation is [227]Th-PSMA-IgG1, a targeted thorium conjugate delivering the alpha particle-emitting radionuclide thorium-227 to PC cells through a conjugated mAb (IgG1) specific for PSMA (Figure 3) [32].
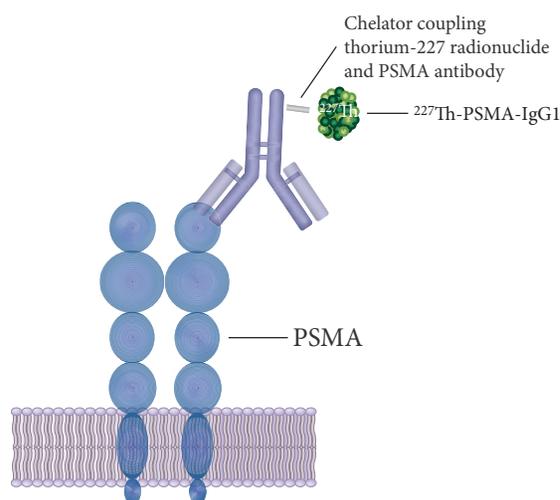

Figure 3. Schematic representation of [227]Th-PSMA-IgG1. An *N*-hydroxysuccinimide-activated 3,2-hydroxypyridinone chelator is coupled to the PSMA antibody and radiolabeled with the thorium-227 radionuclide. PSMA, prostate-specific membrane antigen.

Targeted thorium conjugates are next-generation TαTs that integrate a targeting molecule (e.g. mAb) stably bound to a chelator, and the alpha particle-emitting radioisotope thorium-227 ([227]Th) [114–116] (Figure 3). Thorium-227 is a promising candidate for TαT for its relatively long half-life (18.7 days) and favorable chemical properties that allow stable chelation, preparation, and administration [31, 116]. In addition, thorium-227 decays via alpha particle emission to radium-223, which subsequently decays to stable lead-207; during this process, five alpha particles are released [31].

Preclinical studies showed that [227]Th-PSMA-IgG1 was mainly distributed in tumors, followed by blood, with lower levels of distribution in other tissues (e.g. spleen, kidneys, and liver), indicating highly specific delivery of the alpha therapy to tumors. *In vitro* studies demonstrated that [227]Th-PSMA-IgG1 induced tumor cell death, difficult-to-repair DNA DSBs, and cell cycle arrest in G2/M phase of PC cells. [227]Th-PSMA-IgG1 also induced immunogenic cell death of PC cells. These *in vitro* studies suggest that [227]Th-PSMA-IgG1 may cause cytotoxicity through inducing DNA DSBs in PC cells and potentiation of tumor sensitivity to immunogenic lysis [32].

In vivo studies also demonstrated antitumor activity of [227]Th-PSMA-IgG1 in several PC xenograft models (LNCaP-luc, C4-2, and LAPC-4) and its tolerability (i.e. no significant body weight loss). Tumor growth inhibition was observed with a single dose of [227]Th-PSMA-IgG1 in both PC xenograft models with moderate (22Rv1) and high (MDA-PCa-2b) PSMA expression. In a bone-metastatic PC model, a single dose of [227]Th-PSMA-IgG1 reduced tumor burden, abnormal osteoblastic bone growth, and serum PSA levels [32]. Potent dose-dependent antitumor activity of [227]Th-PSMA-IgG1 was observed in both hormone-sensitive (ST1273) and enzalutamide-resistant (KuCap-1) patient-derived PC xenograft models [33].

Compelling preclinical evidence [32, 33] supports clinical investigation of [227]Th-PSMA-IgG1 for PC, including mCRPC. Further development of other targeted thorium conjugates as precision anticancer modalities to deliver local alpha therapy to other tumor types are ongoing [117–119].

Discussion

Conclusions

TαT has the potential to deliver high-energy alpha radiation selectively to cancer cells and the tumor microenvironment in order to control cancer while minimizing systemic toxicity. The survival benefit and long-term safety profile of radium-223 demonstrated in clinical trials and clinical practice has provided both the proof of concept and real world experience for TαT as a viable therapeutic approach for cancer. Dosimetry calculation and pharmacokinetic measurements of TαT may drive precision medicine-based treatment in a more cost-effective and efficient manner. Potential combination of TαT with chemotherapy, AR-targeting agents, DDR inhibitors, or immuno-oncology drugs may enhance the antitumor activity of each individual therapy through synergistic or complementary interactions, which may expand the clinical utility of TαT in PC. Additionally, PSMA represents a promising therapeutic target for PC. PSMA-targeted

thorium and actinium conjugates are under investigation as next-generation, precision anticancer modalities that deliver local alpha therapy to PSMA-expressing cancer cells.

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