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REVIEW

NAVIGATING THE PROSTATE CANCER FRONTIERS

The advent of Astatine-211 in targeted radionuclide therapy in prostate cancer: will it come to true fruition?

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ABSTRACT

With the growth and surge of prostate cancer theranostics globally, multiple targeted radionuclide therapy (TRT) agents have been utilized to aim to provide a tumoricidal effect to patients who would benefit from TRT. Despite the fact that approved isotopes such as Strontium-89, Samarium-153 and Radium-223 exist, Lutetium-177 prostate specific membrane antigen (PSMA) has revolutionized the impact of radioligand therapy (RLT) in this domain. Key defining clinical trials such as the VISION, TheraP and PSMAfore trials have given clear evidence of the benefit of PSMA RLT in the treatment landscape of metastatic castrate resistant prostate cancer. A number of other radioisotopes in the PSMA RLT domain have also more recently come into the field, notably Terbium-161, Copper- 67 and Iodine-131. Targeted Alpha Therapy (TAT) has grown significantly as well over the last few years owing to physical properties of its high linear energy transfer and DNA damage provided by alpha particles in comparison to beta particles. Actinium-225 PSMA based TAT has formed the basis of prostate cancer theranostics since its initial application, however, many other alpha isotopes are being explored owing to some of the side effects that Actinium-225 presents. Astatine-211, owing to its shorter half-life, has become a more attractive option for its potential utilization in prostate cancer theranostics. Whilst there is preclinical work detailing its efficacy in suppressing tumor growth and limited toxicity profiles, translation into humans is still in its infancy and requires further exploration. A number of clinical trials have utilized Astatine-211 in other malignancies with virtually no work related to prostate cancer. Moreover, the logistics and infrastructure required to support global efforts to make Astatine-211 more readily available should be high on the agenda as well. This narrative review of the literature aims to showcase the current status of Astatine-211 efforts in prostate cancer care with available data (including clinical trials).

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KEY WORDS: Prostatic neoplasms, Astatine-211; Radioisotopes.

Prostate cancer is the second most common cancer presenting in males and the fifth leading cause of cancer death amongst men worldwide.[1] It is estimated that one in five men will develop prostate cancer in a lifetime.[1] Developments in the understanding of the biology of prostate cancer has led to the introduction of novel and effective therapy to improve overall survival in prostate cancer.[2, 3] Routine screening for prostate specific antigen (PSA) remains at the forefront of diagnosis, however, genetic sequencing to understand tumor biology is at the forefront of investigations. Factors that influence the development of prostate cancer are mostly genetic and can be linked to multiple mutations which are continually being explored.[2, 3] The prostate cancer treatment landscape initially entails targeting localized disease with radical prostatectomy, hormonal therapy or radical radiotherapy with or without hormonal therapy. However, even with appropriate primary care, these patients progress. Once the disease becomes metastatic, this is followed by first line hormonal therapy. Patients tend to develop progressive disease after castration and subsequently become castrate resistant. The treatment paradigm of castrate resistant disease includes a myriad of novel anti-androgens and cytotoxic chemotherapy.[2-4] Prostate specific membrane antigen (PSMA), a

750 amino acid transmembrane glycoprotein, is expressed significantly in prostate cancer cells and, as such, targeted therapy utilizing radionuclides has become a significant component of the treatment landscape of metastatic castrate resistant prostate cancer (mCRPC). Prospective trials for targeted PSMA therapy has been demonstrated with beta emitters using Lutetium-177 PSMA ([^{177}Lu]Lu-PSMA).[3, 5-7] Studies such as the VISION trial demonstrated improved overall survival and quality of life in patients who received [^{177}Lu]Lu-PSMA against standard of care.[7] The TheraP study reported significantly improved prostate-specific antigen responses with [^{177}Lu]Lu-PSMA-617 against cabazitaxel in men with metastatic castration-resistant prostate cancer progressing after docetaxel; thereby recommending [^{177}Lu]Lu-PSMA as an alternative to cabazitaxel for PSMA-positive mCRPC progressing after docetaxel.[8] More recently, the PSMAfore trial reported [^{177}Lu]Lu-PSMA-617 prolonged radiographic progression-free survival relative to androgen receptor pathway inhibitors (ARPI) change in patients treated with [^{177}Lu]Lu-PSMA, there by concluding that patients [^{177}Lu]Lu-PSMA may be an effective treatment alternative in patients with PSMA positive mCRPC who are being considered for a change of ARPI after progression on a previous ARPI.[9]

Currently there are a number of trials (Table I) utilizing novel beta emitters in PSMA RLT. The VIOLET trial is of interest owing to the properties of Terbium-161 emitting an Auger electron as well thereby potentially targeting micrometastases.[13] One other trial to note is a Phase II trial utilizing [^{131}I]I-PSMA-1095. Authors in this single-arm, phase 2 trial, aimed to assess efficacy and tolerability of [^{131}I]I-PSMA-1095 in mCRPC patients who had exhausted all lines of approved therapy. They demonstrated that [^{131}I]I-PSMA-1095 is highly active against heavily-pretreated PSMA-positive mCRPC, thereby significantly decreasing tumor burden. Haematological side effects were not completely mitigated owing to potential off-target irradiation.[14]

PSMA RLT, however, can also be achieved with alpha emitters, and these have been utilized to demonstrate treatment response after progression from beta therapy and after failing standard of care in metastatic castrate resistant prostate cancer.[15-17] Key work in chemotherapy naïve patients using Actinium-225 PSMA([^{225}Ac]Ac-PSMA) demonstrated more than 90% decline in serum PSA in 82% of patients with 41% demonstrating undetectable PSA and remission 12 months post targeted alpha therapy (TAT) in this pilot study.[18] The side effect profile is important to keep in mind when using Actinium-225. A recent meta-analysis of xerostomia related treatment side effects utilizing [^{225}Ac]Ac-PSMA as monotherapy reported 84% of patients reporting xerostomia, with 13% of patients reporting Grade 3 xerostomia.[19] Hence the ongoing need for a more optimal PSMA-targeted RLT alpha agent is warranted. The landscape of PSMA TAT with Actinium-225 has laid the foundation for exploration of TRT with other amenable alpha radionuclides, namely, Lead-212 ([^{212}Pb]Pb), Bismuth-213 ([^{213}Bi]Bi), Radium-223 ([^{223}Ra]Ra), Thorium-227 ([^{227}Th]Th), all of which have been labelled with PSMA in the preclinical and clinical setting.[20] Astatine-211, which is one of the newer alpha emitters being explored in TAT has been utilized not only in prostate cancer but explored in a number of other malignancies.[21] Owing to the paucity of data in prostate cancer utilizing Astatine-211, this review aims to paint the narrative for the potential role of Astatine-211 PSMA in prostate cancer TRT.

Literature search

A comprehensive literature search was performed in the PubMed, EbscoHost, Web of Science Scopus, and Cochrane databases to identify articles published up until March 2025 regarding the role of nuclear medicine and molecular imaging and TRT with astatine-211 and prostate cancer. Different combinations of search terms (and their various permutations) were used including “astatine-211,” “prostate cancer,” “metastatic castrate resistant prostate cancer,” “PSMA,”. Editorials and recent conference abstracts were utilized to garner relevant material. The references of the resultant articles were also used to identify

TABLE I.—*PSMA RLT trials utilizing novel beta emitters.*

Trial name	NCT	Phase	Radiopharmaceutical	Outcome (if completed)
ARROW	03939689	2	[^{131}I]I-MPI1095 + Enzalutamide	A statistically significant higher PSA50 (63% *versus* 31%, P=0.003) among subjects who received ^{131}I-LNTH-1095 in addition to standard-of-care enzalutamide.[10]
SECuRE	04868604	1 / 2	[^{67}Cu]Cu-SAR-bisPSMA	No dose limiting toxicities identified with strong preliminary efficacy data demonstrated in the first multidose cohort. Currently dosing for Phase 2.
VIOLET	05521412	1 / 2	[^{161}Tb]Tb-PSMA	The beta radiation absorbed dose following [^{161}Tb]Tb-PSMA I&T are within a safe and expected range for normal organs thus far.[11, 12]

additional manuscripts. A total of 37 key articles were identified that discussed the spectrum of astatine-211 and its impact on prostate cancer theranostics. These articles form the basis of this manuscript.

Key notes on Astatine-211

Astatine is reported to have first been synthesized in 1940, with is first in-human use reported in the early 1950s.[21] Astatine has been described as one of the rarest elements to be found on earth, however, it can be produced in cyclotrons.[21, 22] Astatine-211 [^{211}At]At is an alpha emitting element, undergoing alpha decay (42%), emitting one particle per decay. It has half-life of 7.2 hours which makes it an ideal radiopharmaceutical for radionuclide therapy in comparison to other alpha emitters that have a longer decay series such as [^{227}Th]Th, [^{223}Ra]Ra, [^{212}Pb]Pb, [^{212}Bi]Bi and [^{225}Ac]Ac. The half-life allows for decreased tissue exposure to the isotope but is long enough to ensure shipping from the production site.[21] The one alpha particle per decay may help to simplify dosimetry calculations and evade the potential of exposure to undesirable daughter products. The decay scheme of [^{211}At]At is associated with an alpha decay to Bismuth-207 [^{207}Bi]Bi (half-life 33 years) and electron capture to stable Lead-207 [^{207}Pb]Pb.[22] Astatine can also undergo electron capture (58%) to Polonium-211(half-life 0.53 ms), releasing an alpha particle(7.5MeV) which then becomes stable [^{207}Pb]Pb. Both decay processes produce X-rays which allow for single photon emission computed tomography (SPECT) imaging. Owing to the lack of stable isotopes, Astatine-211 has not been well studied, added to this its complex chemistry. The carbon-astatine bonds are weak which allow for free astatine to abound. As such, free astatine can accumulate in the thyroid gland, stomach, spleen and lung.[20]

Studies related to Astatine-211 in prostate cancer

Preclinical

Limited preclinical work exists detailing the utilization of PSMA RLT (Table II). One of the first studies utilized a urea-based molecule chelated to Astatine-211 ((2*S*)-2-(3-(1-carboxy-5-(4-^{211}At-astatobenzamido) pentyl) ureido)-pentanedioic acid). In the prostate cancer (PCa) xenografts, there was a marked reduction in the growth of the tumor with improved survival in mice who possessed micrometastases.[23]

More recently, Watabe *et al.* developed a PSMA compound based on [^{18}F]F-PSMA1007 for targeting prostate cancer. Of the compounds utilized, their lead compound, PSMA5, was shown to be the most effective in targeting prostate cancer micrometastases.[28] This was followed by another study reviewing the biodistribution and toxicity in a xenograft and primate model in preparation for the first-in-human translation. The results demonstrated

TABLE II.—*Preclinical studies on astatine-211 PSMA.*

Radiopharmaceutical	Tumor model	Key outcome
(2*S*)-2-(3-(1-carboxy-5-(4-^{211}At-astatobenzamido)pentyl)ureido)-pentanedioic acid [^{211}At]At-6)	PC3 PIP Xenograft	Better tumor uptake against comparator at 18 hours. Renal uptake of [^{211}At]-6 was only 50-70% of that observed for ^{131}I-6 at all time points.[23]
[^{211}At]At-RPS-027	LNCaP-xenograft	RPS-027 shows dual targeting to PSMA and albumin, higher tumor uptake, favorable biodistribution.[24]
[^{211}At]At-PSMA-769	PC3 PIP- Xenograft	[^{211}At]At-PSMA-769 uptake in PC3 PIP tumors higher than [^{131}I]I-PSMA-769 at 4 h (9.6±1.6%ID/g *versus* 7.8±1.6%ID/g; lower nephrotoxicity.[25]
[^{211}At]At-B10-Sav-PEGylated LuG/ [^{211}At]At-B10-HAS-PEGylated LuG	C4-2B xenograft	Utilizing PEGylated LuG derivatives to proteins can be an effective mechanism to diminish kidney localization of radiolabeled LuG reagents.[26]
[^{211}At]At-GV-620	PC3 PIP- Xenograft	Good localization in PC3 PSMA+ Improved stability in vivo; higher tumor-to-normal tissue ratios.[27]
[^{211}At]At-PSMA5	LnCaP- xenograft	Higher tumor retention of [^{211}At]At-PSMA5 compared to [^{211}At]At-PSMA-1 and [^{211}At]At-PSMA-6; kidney excretion was better in [^{211}At]At-PSMA-1 compared to [^{211}At]At-PSMA-5 and [^{211}At]At-PSMA-6.[28]
[^{211}At]At-**3**-Lu	PC3 PIP - xenograft	Adequate tumor-to-salivary gland and tumor-to-kidney ratios.[29]
[^{211}At]At-PSAt-3-Ga	LNCaP	Demonstrated increased tumor uptake at 1 h and 24 hours. Uptake in off-target tissues low.[30]
[^{211}At]At-PSMA5	Xenograft Cynomolgus monkeys	No significant myelosuppression or renal dysfunction in the mice. Mild leukopenia 24 h post-administration in the monkeys.[31]
[^{211}At]At-PSMA5 *vs.* [^{225}Ac]Ac-PSMA 617	LNCaP; PC3	^{225}Ac-PSMA-617 nuclide had decreased intracellular uptake with minimal evidence demonstrating uptake by PC3 cells. ^{211}At-PSMA-5 was taken up by PC3 cells and LNCaP cells.[32]

no significant myelosuppression or renal dysfunction in the xenograft model. Mild leukopenia was seen in the primate model 24 hours post administration of [^{211}At]At-PSMA5. However, no severe toxicities were observed in both models.[31]

Kaneda-Nakashima *et al.* has also compared the performance of [^{225}Ac]Ac-PSMA against [^{211}At]At-PSMA5. With varying physical properties and half-lives, Astatine-211 demonstrated no less cytotoxicity when compared to Actinium-225 labelled PSMA, and its shorter half-life does allow for closer dose scheduling potentially.[32] Another group reviewed a novel neopentyl-glycol structure linked to PSMA to enhance in-vivo stability against destination. Higher uptake was seen in the tumor with insignificant uptake in non-target organs such as the thyroid, stomach and salivary glands in xenograft models.[33]

Clinical

Much of the work in clinical translation is seen with many studies using Astatine-211 in a number of other malignancies. These studies have targeted different malignancies, including ovarian cancer, differentiated thyroid cancer, metastatic brain tumors, multiple myeloma and prostate cancer (Table III).[21]

To date, only one case report exists detailing the first-in human translation of [^{211}At]At-PSMA5. This was performed in a patient in their 70s with mCRPC refractory to current standard of care which included androgen receptor signaling inhibitors, docetaxel and cabazitaxel. Post therapy imaging with [^{211}At]At-PSMA5 showed concordant uptake with diagnostic imaging thereby providing proof-of-concept of the theranostic applicability of utilising Astatine-211 PSMA based TAT.[34]

In addition, Japan is leading with a Phase 1 clinical trial (NCT06441994) utilizing [^{211}At]At-PSMA5 as a dose escalation study to ascertain the recommended Phase II dose by reviewing tolerability, safety, pharmacokinetics, absorbed dose, and efficacy of [^{211}At]At-PSMA5.

Future directions and conclusion

Astatine-211 PSMA TAT holds great promise for the clinical domain, particularly in addressing the potential of treating micrometastases in prostate cancer. Astatine-211 TAT is challenged for routine implementation on current production and sourcing of the isotope. The requirement for accelerators that will generators the required 28 – 29MeV alpha particle beam is something to be mindful of.

TABLE III.—*Astatine-211 clinical trials in the public domain, available from clinicaltrials.gov.*

Institution	Malignancy	Status of trial	Study objective(s)	Target	Primary outcome
Gothenburg, Sweden NCT04461457	Ovarian cancer	Completed	Treatment Early phase 1	MX-35 F(ab')2	Maximum concentration of At-211 Area under curve (AUC) of At-211 Toxicity
Osaka University Hospital NCT05275946	Differentiated Thyroid cancer	Recruiting	Treatment	NIS	Treatment related adverse events Dose limiting toxicity
Duke University NCT00003461	Primary or Metastatic Brain tumors	Completed	Toxicity Therapeutic treatment response	Monoclonal antibody 81C6	Dose escalation
Osaka University Hospital NCT06441994	Prostate cancer	Recruiting	Treatment	PSMA	Treatment related adverse events Dose limiting toxicity
Fred Hutchinson Cancer Centre NCT04083183	Non-malignant neoplasm	Suspended pending FDA clinical hold	Treatment	Monoclonal antibody BC8-B10	Graft rejection
Fred Hutchinson Cancer Centre NCT04466475	multiple myeloma	Withdrawn	Treatment	Monoclonal antibody OKT10-B10	Maximum tolerated dose
Fred Hutchinson Cancer Centre NCT04579523	Newly diagnosed, recurrent, or refractory high-risk multiple myeloma	Not yet recruiting	Treatment	Monoclonal antibody OKT10-B10	Maximum tolerated dose
Fred Hutchinson Cancer Centre NCT03670966	Relapsed or refractory high-risk acute leukemia or myelodysplastic syndrome	Recruiting	Treatment	Monoclonal antibody BC8-B10	Toxicity

More work into investing in capable infrastructure to make this a reality is required for the long-term longevity of astatine-211 in strategic locations globally for widespread implementation. Currently only 15 countries are actively producing Astatine-211.[35]

From a preclinical perspective, more work is required to translating compounds into first-in-human studies that will allow mapping of safety profiles and optimizing doses that would be required to garner a good clinical outcome, particularly making sure non-target organs are not unnecessarily irradiated.

Continued support from international consortia and similar organizations (*e.g*. network for optimized astatine-labeled radiopharmaceuticals (NOAR) needs to be top priority to allow for accelerated implementation worldwide.[36] As the treatment landscape of prostate cancer expands, it is likely, despite the current shortcomings, that Astatine-211 will become a key part in the armamentarium of available radio nuclides for clinical translation.[37]

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
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