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Professional Paper

PROSTATE CANCER THERANOSTICS – CURRENT EVIDENCE AND FUTURE CONSIDERATIONS: A BRIEF OVERVIEW

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SUMMARY – Despite initial response to androgen inhibition, metastatic prostate cancer is invariably an incurable disease. New agents with different mechanisms of action are needed that are capable of producing clinical benefit and prolonging survival. New breakthroughs specific to prostate cancer are being made by combining novel diagnostic molecular imaging modalities with cytotoxic radionuclide payloads to cancer cells and the surrounding tumor microenvironment. This concept yielded unprecedented clinical responses in a very challenging population of patients. Targeted radionuclide therapy, mainly targeting prostate-specific antigen (PSMA), is now considered the new standard of care for patients with advanced disease who have progressed to the use of new androgen suppressors and chemotherapy. Targeted radionuclide therapy, mainly focused on prostate-specific antigen, is now considered the new treatment standard for patients with more aggressive disease who have been treated with new androgen suppressors and chemotherapy. The application of the theranostic paradigm has enabled personalized management of prostate cancer patients, with significant potential for future development in the form of a combination therapy with other agents. This freeform review article summarizes the key clinical research in the field of radionuclide targeted therapy for prostate cancer and provides an overview of current practice in this rapidly evolving entity.

Key words: *prostate-specific membrane antigen (PSMA); peptide; radionuclide; radiotherapy; alpha particle; prostate cancer; castration resistance*

Introduction

The term theranostics is used in nuclear medicine to describe a combination of therapy and diagnostic imaging. The basic principles of theranostics have been applied in the imaging and treatment of thyroid diseases for more than 70 years. Theranostics dates back to 1941, when radioactive sodium iodide (I-131) was first used to treat patients with hyperthyroidism and thyroid cancer. In 1951, the US Food and Drug Administration (FDA) approved sodium iodide (I-131) for use in patients with thyroid disease. It was the first radiopharmaceutical to be approved by the FDA.

More recently, the most successful examples of theranostics were peptide receptor scintigraphy (PRS) and peptide receptor radionuclide therapy (PRRT) of

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neuroendocrine tumors (NETs). Following the discovery of the presence of somatostatin receptors on the cell surface of intestinal NETs, radiolabeled somatostatin analogues were developed. The development of these modalities has revolutionized patient management and laid the foundations for the extension of the theranostic principle to other oncological indications. The first use of PRS and PRRT in patients with NETs dates back to the late 1980s[1-3]. Steven Lamberts and Jean Claude Reubi presented their data at a postdoctoral meeting. They used an octreotide linked to the iodine isotope 125I and were the first to demonstrate the presence of somatostatin receptors on the cell surface of intestinal NETs[3,4]. Eric Krenning, after seeing this data, recognized the potential of using radiolabeled peptides to localize and treat NETs in the clinical setting[3]. In 1987, after a period of attempts to produce a suitable radioiodine-labelled peptide for human imaging, SPECT images of a patient with NET were finally obtained. Subsequently, the use of radioiodine-labelled peptides spread worldwide.

Treating patients with metastatic castration-resistant prostate cancer (mCRPC) remains very challenging despite the wide use of many drugs to slow progression and prolong life[5,6].

Metastatic prostate cancer is mostly found in the bones. In metastatic prostate cancer, the complex microenvironment in the bone is disrupted by growth factors released by prostate cancer[7-10]. In addition, osteoblasts may also express growth factors that stimulate prostate cancer cell growth, creating a cycle of disorganized bone metabolism[10].

Role of prostate-specific membrane antigen (PSMA) in theranostics

PSMA, also known as folate hydrolase I, glutamate carboxypeptidase II, and N-acetyl-L-aspartyl-L-glutamate peptidase I (NAALDase), has several biological characteristics that make it an ideal target structure for radiopharmaceutical development[11,12]. PSMA shows significant overexpression on most prostate cancer cells, especially those at an advanced stage[11], and there is also a correlation between PSMA and cancer stage and grade, showing increased PSMA levels in higher stages and grades[13-15].

Two different approaches have been used to target PSMA. The first approach uses the molecular structure of the PSMA protein and labels specific monoclonal antibodies as the targetable vehicles[15,16]. The other uses the enzymatic activity of PSMA and uses radiolabeled inhibitors or enzyme binders as the targetable vectors[15,17]. The second approach has recently been gaining increasing popularity. There are multiple reasons for this. Firstly, small molecules are rapidly eliminated from the blood. In addition, when radiolabeled small molecules are used, internalization via clathrin-coated wells occurs once the ligand binds to the target[15,18]. This results in efficient transport of the bound molecule into the cell, resulting in increased uptake and retention in the tumor[15].

Theranostics requires three elements: a target (for example PSMA), a target agent (for example PSMA-617), and a therapeutic target payload (for example ^{117}Lu).

For PSMA 617, a beta emitter such as Lu-177 or an alpha emitter such as Ac-225 can be used. First, the target must be imaged using a PSMA PET/CT, and it is then treated with one of the therapeutic agents.

The first drug approved for theranostics was ^{177}Lu-PSMA-617. The payload of this agent is the beta emitter ^{177}Lu, which causes the destruction of the targeted cancer cells and several other surrounding cells. These drugs bind to PSMA receptor, and the cell then endocytoses the drug, thus introducing the target agent and payload into the cell. The drugs are then deconjugated inside, separating the target agent and the therapeutic payload, and radiation is delivered into the cell, killing the cells. After that, the drugs are eliminated by the body.

The primary trial that led to the regulatory recognition of ^{177}Lu-PSMA-617 was the VISION trial[19]. The key eligibility criteria for this trial was PSMA imaging. All patients in this study underwent a ^{68}Ga-PSMA-11 PET/CT scan. To be included in this trial, patients had to have had a disease that was PSMA-avid. The criteria were: patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with one or more androgen receptor pathway inhibitors and 1 or 2 lines of taxane chemotherapy, good performance status, and a life expectancy of more than 6 months[19]. The patients were classified into two groups: the first group received standard treatment alone, the second group received standard treatment plus ^{177}Lu-PSMA-617[19]. The standard treatment could not be chemotherapy, immunotherapy, or radium-223, or other investigational drugs, because the safety profile of the combination of these drugs was unknown[19]. There were two pri-

mary endpoints: the first was radiographic progression-free survival (rPFS), and the second was overall survival (OS).

What were the treatment standards?

At this point in treatment planning for patients with mCRPC, our treatment strategies are very limited, making this patient population difficult to treat.

The dosing regimen of ^{177}Lu-PSMA-617 was 4-6 doses administered every 6 weeks[19]. Four doses were standard, and patients could receive an additional two doses if they seemed to be doing well. Results showed a 38% reduction in the risk of death, a 60% reduction in the risk of disease progression or death, and a 50% reduction in the risk of a symptomatic skeletal event in the ^{177}Lu-PSMA-617 patient group[19].

The median overall survival was 11.3 months in the control group and 15.3 months in the experimental group. In the majority of patients in the control group, the disease had progressed after 3.4 months, while in patients in the experimental group it had progressed after 8.7 months[19].

Quality of life was maintained in the experimental group, as was the delay in the onset of new pain. The time to worsening of pain intensity was 14.3 months in the experimental group and 2.9 months in the control group[19].

Patients who received androgen receptor signal inhibitor (ARSI) therapy as the combination of choice in addition to Lutetium therapy appeared to be better off than those who received other therapies in combination with ^{177}Lu-PSMA-617[19].

Who should receive PSMA-directed theranostic treatment?

It must be recognized that there are patients who do not respond to this treatment. The complete response (CR) rate was 9.2%, the partial response (PR) rate was 41.8%, and about 50% of patients did not respond to treatment because they had either stable disease or advanced disease. The key question in the development of theranostics is how we can achieve better outcomes. Who should receive ^{177}Lu-PSMA-617?

In a paper published in the Lancet Oncology journal, Andrei Gafita et al. presented a nomogram predicting the outcomes of ^{177}Lu treatment[20]. They proposed a nomogram that can help us decide which patients should receive ^{177}Lu-PSMA-617. Among the criteria in this nomogram were some traditional clinical prognostic variables (time since diagnosis, history of chemotherapy treatment, liver metastases, level of hemoglobin) combined with new prognostic variables relevant to this patient population: PSMA expression in the tumor, number of PSMA-positive metastatic lesions, tumor mean standardized uptake value (SUV_{mean}), and the site of disease based on the TNM classification system with molecular imaging[20,21]. In this nomogram, SUV_{mean} was prognostic and predictive for ^{177}Lu-PSMA-617 treatment, because it determines the dose that is going to be delivered to the target lesion.

Alpha emitters

It has been shown that dose is important for the response to treatment with ^{177}Lu-PSMA-617[22]. There is a significant relationship between the whole body tumor dose and PSA response. Patients receiving less than 10 Gy were less likely to have a PSA drop of at least 50%[22].

Research has therefore focused on alpha emitters such as actinium. Actinium has great potential, not only as a first-line treatment but also as a rescue therapy after ^{117}Lu treatment failure. Ac-225 is an alpha emitter; it releases more energy but across a shorter pathway (high linear energy transfer), and it was considered that by using an alpha emitter we could increase the dose without adverse consequences such as hematological toxicities[15]. The clinical data reported so far are promising, but it should be remembered that the use of alpha emitters not only increases the dose to the tumor site but also to the salivary glands, causing xerostomia, which is a dose-limiting factor[15].

Mechanisms of resistance

What are the mechanisms of disease resistance? PSMA expression can vary not only between patients, but also within one patient[23]. To simplify: we see what we treat, and we treat what we see.

The other mechanism of resistance is genetic. Patients with TP53 mutations have been shown to be less likely to respond to therapy with PSMA-targeted theranostics[24]. It is also suspected that patients with mutations in DNA damage repair enzymes may be more sensitive to theranostics, although this has not yet been proven.

Optimization strategies

PSMA PET/CT also has a role in predicting who will benefit more from theranostics treatment. In 2021, Michael Hofman et al. published the TheraP study. This was a multicenter, unblinded, randomized phase 2 study with two arms. The male participants were allocated randomly to one of the following options: ^{177}Lu PSMA-617 or cabazitaxel[25]. Although updated results after three years of follow-up showed similar OS compared with cabazitaxel, it also showed that PSMA PET can predict who will respond better to ^{177}Lu PSMA-617 and who will not. The higher the avidity of PSMA PET, the more likely the patient is to respond to PSMA-targeted therapy. In conclusion, a PSMA PET/CT scan should be performed before deciding on theranostics treatment.

Future directions

When a new drug is developed, it is usually first used in the later stages of a disease. Once it has proven successful in the later stages, it can also be used in earlier stages of the disease. The PSMAfore study is one of the first studies to move theranostic treatment to earlier stages of the disease. Patients with mCRPC with disease progression after androgen deprivation therapy (ADT) and androgen receptor pathway inhibitor (ARPI) therapy, and whose PSMA scan shows PSMA-avid disease but who have not yet received chemotherapy were recruited for the study and set to receive either six cycles of ^{117}Lu-PSMA-617 or another ARPI treatment.

The primary endpoint was rPFS rather than OS, because the trial allowed crossover upon radiographic progression. We are still awaiting the results of this study.

Another similar trial is the SPLASH trial, which uses ^{177}Lu-PNT2002. The eligibility criteria were: mCRPC, PSMA-avid PET, progression on androgen receptor axis therapy (ARAT), and no previous history of chemotherapy treatment. Patients were randomly divided into two groups in a 2:1 ratio, the first being the experimental arm, and the second being the control arm that received abiraterone or apalutamide. rPFS is the primary endpoint, and this study is still enrolling patients.

EnzaP (ANZUP 1901) is also investigating the first-line treatment for mCRPC. Patients that are enrolled must have chemotherapy-naive mCRPC, baseline PSMA PET SUV_{max} more or equal to 10, prostate-specific antigen (PSA) levels above 5 ng/mL, and 2 or more characteristics at a high risk of early failure of enzalutamide therapy. Subjects are to be randomized (1:1) to receive enzalutamide 160 mg daily or enzalutamide alone plus ^{177}Lu-PSMA-617 7.5 GBq on days 15 and 57. Two subsequent doses of ^{177}Lu-PSMA-617 are allowed, which are informed by positron emission tomography (PET) with gallium-68 (^{68}Ga)-PSMA on day 92, with up to four doses in total. The primary endpoint is progression-free survival (PFS), which is characterized by prostate-specific antigen (PSA). Other major endpoints include radiological PFS, PSA response rate, overall survival, health-related quality of life, adverse events, and cost-effectiveness. We are still awaiting the results of this trial.

There is also an ongoing trial for ^{117}Lu-PSMA-617 in newly-diagnosed metastatic hormone-sensitive disease (mHSPC) called PSMA Addition. Patients will receive appropriate standard of care (ADT and ARPI) with or without ^{117}Lu-PSMA-617. Crossover is permitted upon radiographic progression, and the primary endpoint is rPFS. These results will be available in the years to come.

The UpFront PSMA trial is also recruiting patients with mHSPC, but, in contrast to PSMA Addition, patients will get docetaxel followed by ^{117}Lu-PSMA-617 or docetaxel alone. The primary endpoint is undetectable PSA levels after 12 months. This study is still open for enrollment.

Clinically localized disease is the most challenging disease for the introduction of theranostics. The advantage of introducing it at these stages is that theranostics may be able to cure the disease, which is an unlikely outcome in advanced disease. Therefore, this stage is the most attractive, but also the most difficult for the implementation of the treatment. If a patient has early metastatic disease that can only be demonstrated by PSMA PET/CT, this patient could potentially be saved by radical prostatectomy, and post-operatively the widespread disease could be treated with a circulating drug that would deliver radiation to the tumor site.

What will be the endpoint of these trials? For late-stage disease, we have OS, rPFS, quality of life improvement, but we do not currently have a suitable endpoint for early-stage disease. In early stages, OS can be several years and quality of life improvement can be valuable, but many patients are asymptomatic

as they have a low disease burden. In addition, most patients do not have measurable disease and, as we already know, PSA is not a suitable endpoint in clinical trials as is not related to OS. Therefore, much remains to be done to introduce theranostics in the earlier stages of the disease.

Conclusion

Over the last decade, theranostic agents that precisely target specific molecular features of prostate cancer have been successfully developed and are currently being used clinically to detect, image-guide, and provide tailored treatment for men with metastatic prostate cancer. The bulk of the activity has been focused on castration-resistant disease, where the theranostic concept has prolonged the life of patients who previously had limited treatment options. The cornerstone of targeted treatment is PSMA-bonded therapy. PSMA is an ideal target for theranostics given its widespread presence across the disease spectrum in men with prostate cancer. Rapid development spurred novel clinical trials with innovative concepts, testing new theranostic approaches in addition to standard anti-cancer therapy aiming to improve quality of life and overall survival. These novel agents have the unique capacity to deliver ablative doses of radiation to disease sites throughout the body with the potential to overcome therapeutic resistance. In the future, radio-targeted agents will probably be integrated with current treatment modalities and approved molecular imaging methods to treat prostate cancer with higher physical and biological precision.

References

1. Krenning EP, Bakker WH, Breeman WA, et al. Localization of endocrine-related tumours with radioiodinated analogue of somatostatin. Lancet. 1989;1(8632):242-44. doi: 10.1016/s0140-6736(89)91258-0.
2. Krenning EP, Kooij PP, Bakker WH, et al. Radiotherapy with a radiolabeled somatostatin analogue, [111In-DTPA-D-Phe1]-octreotide. A case history. Ann N Y Acad Sci. 1994;733:496-506. doi: 10.1111/j.1749-6632.1994.tb17300.x.
3. Levine R, Krenning EP. Clinical History of the Theranostic Radionuclide Approach to Neuroendocrine Tumors and Other Types of Cancer: Historical Review Based on an Interview of Eric P. Krenning by Rachel Levine. J Nucl Med. 2017;58(Suppl 2):3S-9S. doi: 10.2967/jnumed.116.186502.
4. Reubi JC, Häcki WH, Lamberts SW. Hormone-producing gastrointestinal tumors contain a high density of somatostatin receptors. J Clin Endocrinol Metab. 1987;65(6):1127-34. doi: 10.1210/jcem-65-6-1127.
5. Sartor O, de Bono JS. Metastatic Prostate Cancer. N Engl J Med. 2018;378(7):645-57. doi: 10.1056/NEJMra1701695.
6. Nuhn P, De Bono JS, Fizazi K, et al. Update on Systemic Prostate Cancer Therapies: Management of Metastatic Castration-resistant Prostate Cancer in the Era of Precision Oncology. Eur Urol. 2019;75(1):88-99. doi: 10.1016/j.eururo.2018.03.028.
7. Body JJ, Casimiro S, Costa L. Targeting bone metastases in prostate cancer: improving clinical outcome. Nat Rev Urol. 2015;12(6):340-56. doi: 10.1038/nrurol.2015.90.
8. Casimiro S, Guise TA, Chirgwin J. The critical role of the bone microenvironment in cancer metastases. Mol Cell Endocrinol. 2009;310(1-2):71-81. doi: 10.1016/j.mce.2009.07.004.
9. Ottewell PD. The role of osteoblasts in bone metastasis. J Bone Oncol. 2016;5(3):124-7. doi: 10.1016/j.jbo.2016.03.007.
10. O'Dwyer E, Bodei L, Morris MJ. The Role of Theranostics in Prostate Cancer. Semin Radiat Oncol. 2021;31(1):71-82. doi: 10.1016/j.semradonc.2020.07.004.
11. Pillai MRA, Nanabala R, Joy A, Sasikumar A, Russ Knapp FF. Radiolabeled enzyme inhibitors and binding agents targeting PSMA: Effective theranostic tools for imaging and therapy of prostate cancer. Nucl Med Biol. 2016;43(11):692-720. doi: 10.1016/j.nucmedbio.2016.08.006.
12. Bouchelouche K, Turkbey B, Choyke PL. PSMA PET and Radionuclide Therapy in Prostate Cancer. Semin Nucl Med. 2016;46(6):522-35. doi: 10.1053/j.semnuclmed.2016.07.006.
13. Berger I, Annabattula C, Lewis J, et al. ^{68}Ga-PSMA PET/CT vs. mpMRI for locoregional prostate cancer staging: correlation with final histopathology. Prostate Cancer Prostatic Dis. 2018;21(2):204-11. doi: 10.1038/s41391-018-0048-7.
14. Li R, Ravizzini GC, Gorin MA, et al. The use of PET/CT in prostate cancer. Prostate Cancer Prostatic Dis. 2018;21(1):4-21. doi: 10.1038/s41391-017-0007-8.
15. Chakravarty R, Siamof CM, Dash A, Cai W. Targeted α-therapy of prostate cancer using radiolabeled PSMA inhibitors: a game changer in nuclear medicine. Am J Nucl Med Mol Imaging. 2018;8(4):247-67.
16. Jindal V. Immunotherapy: a glimmer of hope for metastatic prostate cancer. Chin Clin Oncol. 2018;7(6):61. doi: 10.21037/cco.2018.02.01.
17. Udovicich C, Perera M, Hofman MS, et al. ^{68}Ga-prostate-specific membrane antigen-positron emission tomography/computed tomography in advanced prostate cancer: Current state and future trends. Prostate Int. 2017;5(4):125-9. doi: 10.1016/j.prnil.2017.02.003.
18. Pillai MRA, Nanabala R, Joy A, Sasikumar A, Russ Knapp FF. Radiolabeled enzyme inhibitors and binding agents targeting PSMA: Effective theranostic tools for imaging and therapy of prostate cancer. Nucl Med Biol. 2016;43(11):692-720. doi: 10.1016/j.nucmedbio.2016.08.006.
19. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2021;385(12):1091-103. doi: 10.1056/NEJMoa2107322.
20. Eiber M, Herrmann K, Calais J, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): Proposed miTNM Classification for the Interpretation of PSMA-Ligand PET/CT. J Nucl Med. 2018;59(3):469-78. doi: 10.2967/jnumed.117.198119.

21. Gafita A, Calais J, Grogan TR, et al. Nomograms to predict outcomes after ^{177}Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study. Lancet Oncol. 2021;22(8):1115-25. doi: 10.1016/S1470-2045(21)00274-6.
22. Violet J, Jackson P, Ferdinandus J, et al. Dosimetry of ^{177}Lu-PSMA-617 in Metastatic Castration-Resistant Prostate Cancer: Correlations Between Pretherapeutic Imaging and Whole-Body Tumor Dosimetry with Treatment Outcomes. J Nucl Med. 2019;60(4):517-23. doi: 10.2967/jnumed.118.219352.
23. Iravani A, Violet J, Azad A, Hofman MS. Lutetium-177 prostate-specific membrane antigen (PSMA) theranostics: practical nuances and intricacies. Prostate Cancer Prostatic Dis. 2020;23(1):38-52. doi: 10.1038/s41391-019-0174-x.
24. Stuparu AD, Capri JR, Meyer CAL, et al. Mechanisms of Resistance to Prostate-Specific Membrane Antigen-Targeted Radioligand Therapy in a Mouse Model of Prostate Cancer. J Nucl Med. 2021;62(7):989-95. doi: 10.2967/jnumed.120.256263.
25. Hofman MS, Emmett L, Sandhu S, et al. [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet. 2021;397(10276):797-804. doi: 10.1016/S0140-6736(21)00237-3.

Sažetak

TERANOSTIKA RAKA PROSTATE - TRENUTNI DOKAZI I BUDUĆI ASPEKTI. KRATKI PREGLED

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Unatoč početnom odgovoru na liječenje inhibitorima androgenog receptora, metastatski kastracijski-rezistentni rak prostate u pravilu je neizlječiva bolest. Potrebni su novi lijekovi s različitim mehanizmima djelovanja koji mogu dovesti do kliničke koristi i produljenja preživljenja. U raku prostate, recentno je došlo do važnih otkrića koji uključuju nove dijagnostičke metode molekularnog oslikavanja kombinirane sa ciljanom radionuklidnom terapijom. Ovaj koncept je dao važne pomake u liječenju u vrlo izazovnoj populaciji pacijenata. Ciljana radionuklidna terapija, uglavnom usmjerena na prostata specifičan membranski antigen (PSMA), sada se smatra novim standardom liječenja za bolesnike s uznapredovalom bolesti kod kojih je došlo do progresije bolesti nakon hormonske terapije i kemoterapije. Primjena teranostičke paradigme omogućila je personalizirano liječenje bolesnika s rakom prostate, sa značajnim potencijalom za budući razvoj u obliku kombinirane terapije s drugim lijekovima. Ovaj pregledni članak sažima ključna klinička istraživanja u području radionuklidne ciljane terapije za rak prostate i daje pregled trenutne prakse u ovom području koje se brzo razvija

Ključne riječi: *prostata-specifični membranski antigen (PSMA), peptid, radionuklid, radioterapija, alfa čestica, karcinom prostate, otpornost na kastraciju*