Review

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Prostate-specific Membrane Antigen-Based Nanomedicine Applications in the Diagnosis and Treatment of Prostate Cancer

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Abstract

Nanomedicine is a branch of nanotechnology that includes the development of nanostructures and nanoanalytical systems for various medical applications. The rapid development of nanomedicine offers new possibilities in cancer diagnosis and treatment. New therapeutic strategies in cancer research using nanoparticles are being developed in order to improve the specificity and efficacy of drug delivery, thus reaching maximal effectiveness with minimal side effects. Due to its selective overexpression in prostate cancer (PCa), prostate-specific membrane antigen (PSMA) has been recognized as a highly promising target for diagnostic and therapeutic applications. This review provides an update on the PSMA-based nanomedicine applications in PCa.

Keywords: Prostate cancer, PSMA, nanomedicine, nanotechnology, theranostic concepts

Introduction

Theranostic Concept

Targeted cancer therapy can improve progression-free and overall survival. However, the greatest barrier to targeted therapy is identifying the patients who will benefit from it. Therefore, predictive markers are urgently needed. Radiolabeled probes can be used as predictive markers. For instance, target expression can be confirmed by positron-emitting tomography (PET) using F-18- or Ga-68-labeled ligands. The same ligands can be labeled with therapeutic radionuclides (Lu-177/Y-90) for radioligand therapy (RLT). This combination is called a theranostic pair.

Nuclear medicine specialists used this method with I-131 to treat metastatic thyroid adenocarcinoma in 1946 (1). By using I-131 in diagnostic screening, they were able to identify patients with differentiated thyroid carcinoma who would benefit from treatment with a higher dose of I-131 (2). In the 1990s, the theranostic approach progressed toward neuroendocrine tumors (NET). Somatostatin analogs DOTATOC, DOTANOC, and DOTATE were developed to selectively bind to NETs overexpressing somatostatin receptors (SSTR) (3,4,5). Labeling these SSTR agonists with different radionuclides enabled the combination of diagnostic imaging (Ga-68) with radioligand treatment (Lu-177/Y-90) (3,4,5). NETTER-1 was the first randomized prospective study comparing Lu-177-labeled DOTATE with octreotide long-acting repeatable (LAR) in metastatic NET. Lu-DOTATE RLT significantly prolonged progression-free survival (PFS) compared to octreotide LAR (6). Progression was 4.8-fold more frequent among patients who received high-dose octreotide than in those given Lu-177DOTATE (HR: 0.21, 95% CI: 0.13-0.34) (6). This treatment is currently known as peptide receptor radionuclide therapy (PRRT) and is widely accepted and used in patients with NET (5).

Prostate-specific Membrane Antigen as a Target in Prostate Cancer

Prostate-specific membrane antigen (PSMA), also known as glutamate carboxypeptidase II, is a promising theranostic target (7-9). PSMA is a type II transmembrane protein comprised of a small intracellular segment, a transmembrane domain, and an extracellular domain containing the catalytic site (8,9). PSMA is expressed at low levels in various tissues such as prostate, brain, small intestine, and kidney (8,9). While PSMA has different enzymatic functions in brain and small intestine, its enzymatic function in the prostate is not yet clear (9). Most importantly, PSMA is overexpressed in prostate cancer cells and its expression

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level is correlated with pathological grade (10,11,12,13,14,15). Moreover, after ligand binding, PSMA is internalized via clathrin-coated pits and endocytosis (11,16). These characteristics have led to the development of therapeutic PSMA ligands labeled with different radionuclides.

PSMA-targeted Agents

One of the first probes that targeted PSMA was Indium-111 capromab pendetide (ProstaScint®). Capromab is a monoclonal antibody that binds to the cytoplasmic domain of PSMA (16). Probes that target the extracellular domain of PSMA, such as antibody J591, have been developed to improve tumor uptake. However, antibody-based approaches have limited diagnostic potential (8). In recent years, nanoparticle PSMA ligands have been developed. One of these is Ga-68-PSMA-11, which is the most commonly used PET probe in PSMA-based imaging (17). Ga-68-PSMA-11 shows excellent biodistribution and high tumor uptake (18). However, PSMA-11 cannot be labeled with Lu-177 or Y-90 for RLT (19). Therefore, nanoparticle ligands with different chelators were developed. Weineisen et al. (19,20) synthesized DOTAGA-FFK (Sub-KuE), which can be labeled with Ga-68 or Lu-177/Y-90, and its optimized version, PSMA I&T. PSMA I&T has good dosimetry and similar biodistribution to Ga-68-PSMA-11 (20). A research group in Heidelberg also developed PSMA-617, which can be labeled with Ga-68 or Lu-177/Y-90. This probe showed high affinity to PSMA and high tumor base uptake (21,22). Based on their similar biodistribution, PSMA-11 and PSMA-617 are frequently used in combination as diagnostic and therapeutic agents (22). Moreover, commercial ligands labeled with Tc-99m or I-131 have been developed as theranostic pairs (23,24). Mease et al. (25) and Cho et al. (26) synthesized 18-FDCFBC, which is an F-18-labeled small-molecule PSMA inhibitor. This agent reliably detects prostate cancer. The second-generation probe 18-FDCFPyL has shown higher affinity for PSMA and tumor uptake than 18-FDCFBC (27). This probe has good dosimetry and biodistribution, but cannot be labeled with Lu-177 or Y-90 for RLT (28).

Here we present an overview of PSMA-targeted diagnosis and RLT.

PSMA Imaging for Primary Diagnosis

Imaging serves two purposes in the primary diagnosis of prostate cancer. The first is to detect disease progression in patients who have biopsy-proven disease or high metastasis risk, and the second is to determine primary tumor location in patients with high suspicion but negative biopsy (29). Magnetic resonance imaging (MRI) is currently the preferred modality for T staging (29). T2-weighted, dynamic contrast-enhanced, and diffusion-weighted sequences are used to identify tumor involvement, extracapsular extension, seminal vesicle invasion, and/or other organ involvement. Moreover, combining these protocols with multiparametric MRI (MP-MRI) enables the differentiation of benign and malignant prostate tissue (30). MRI is superior to C-11-choline PET/CT (31,32,33), FDG-18 PET/CT (31), and ultrasound-guided biopsy (34) for primary diagnosis.

PSMA PET Imaging for T Staging

Rowe et al. (35) reported that MRI had higher sensitivity in the detection of primary lesions compared to F-18-DCFBC PET/CT. The importance of the second-generation radionuclide tracer F-18-DCFPyL in the detection of primary prostate lesions has not yet been evaluated. Ga-68-PSMA-11 PET is superior to MP-MRI, with a sensitivity of 49-76% in different populations (36,37). Ga-68-PSMA-11 uptake was found to be significantly higher in histopathology-positive areas than negative areas (37). The accuracy of GA-68-PSMA-11 PET/CT in the detection of seminal vesicle invasion and extracapsular tumor spread was 86% and 71%, respectively (37). Based on these findings, PSMA imaging has the potential to replace MP-MRI for determining tumor location.

Clinically, treatment options for localized prostate cancer may vary from active surveillance to radiotherapy and radical prostatectomy. T staging is important for determining the best approach. European Association of Urology guidelines recommend MP-MRI for T staging (29), and although PSMA is superior in the detection of primary prostatic lesions, increased diagnostic accuracy has not been shown to have a significant effect on patient management. Of 15 patients who underwent MRI and were diagnosed with prostate cancer, planned radiotherapy was changed in 26.4% after additional PSMA imaging (additional dose, wide area) (38). However, due to inadequate long-term follow up and lack of a control group, the effects of these findings on patient outcomes are not known. Therefore, further studies are required to determine whether PSMA PET influences clinical management at initial diagnosis of patients with prostate cancer.

PSMA Imaging for N Staging

Many studies have demonstrated high reliability of Ga-68-PSMA-11 PET/CT in N-staging at primary diagnosis. Budäus et al. (39) retrospectively compared lymph node findings in preoperative Ga-68-PSMA-11 PET/CT with histopathology in 12 patients and reported a low detection rate of 33.3% and mean sizes of detectable and undetectable lymph nodes of 13.6 mm and 4.3 mm, respectively. Later studies showed that Ga-68-PSMA-11 PET/CT or PET/MRI were superior to conventional imaging techniques in the detection of lymph nodes (40,41,42). In one study, lymph node metastasis was detected using Ga-68-PSMA-11 PET/CT in 12 patients in whom conventional imaging modalities did not show lymph node involvement (40). Herleman et al. (41) demonstrated that the accuracy of Ga-68-PSMA-11 PET/CT (88%) was superior to that of CT (77%). More importantly, 40% of the lymph nodes detected via Ga-68-PSMA-11 PET/CT were reported to have short axis lengths of <5 mm (41). In a prospective study including 30 moderate/high-risk patients, the mean diameters of lymph nodes that were actually detected and those that could not be detected using Ga-68-PSMA-11 PET/CT were 4.7 mm and 2.7 mm, respectively (42). None of the currently available imaging modalities are able to accurately detect lymph nodes because of their size. However, PSMA PET is superior to conventional imaging methods in the detection of lymph nodes. With the exception of the study by Maurer et al. (40), its

specificity and sensitivity were higher than CT and MRI. PSMA PET imaging has the potential to determine N stage and thus to change initial prostate cancer stage.

PSMA Imaging for M Staging

In all previous studies, Ga-68-PSMA-11 PET/CT was used for whole-body screening. PSMA imaging detects bone and visceral metastases more accurately than conventional imaging modalities (CT and bone scintigraphy). In a retrospective study including 126 patients, Ga-68-PSMA-11 PET/CT detected osseous metastases with 99% sensitivity and 88% specificity, whereas these rates were 87% and 61% in bone scintigraphy, respectively (43).

Although PSMA PET imaging is better in M staging, it is not yet clear whether this advantage makes a positive impact in patient management.

Limitations of PSMA PET in Primary Staging

Firstly, PSMA expression in primary lesions is variable and heterogeneous, and thus, sensitivity is limited (44). Moreover, benign diseases such as prostate hyperplasia are associated with high PSMA expression and have the potential to reduce specificity (45,46). Although PSMA PET is more reliable in TNM staging compared to conventional methods, studies focusing on the clinical effect of Ga-68-PSMA-11 PET/CT at primary diagnosis are needed.

PSMA Imaging for Biochemical Recurrence

The risk of biochemical recurrence of prostate cancer is 15-20% within 5 years of first treatment and 25-30% within 10 years (47,48). Correct diagnosis and tumor location are essential because clinical management varies from active surveillance to local/systemic treatment (29). Despite important advances in imaging methods, determining the location of recurrences remains a major challenge. For patients with elevated PSA or clinical symptoms, current guidelines recommend either radionuclide bone scintigraphy, abdominopelvic CT, MP-MRI, or choline/acetate PET/CT (29). However, the recommended imaging modalities have limited detection rates (29,24). In patients with serum PSA level <7 ng/mL, the probability of having a positive bone scintigraphy is <5% (29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51). CT is positive in only 11-14% of patients with biochemical recurrence (51). Moreover, in a study of 132 patients, it was reported that in order for CT to be positive, the mean PSA value must be 27.4 ng/mL (51). In patients with high-risk prostate cancer, MRI and choline PET/CT were reported to have comparable sensitivity in the detection of bone metastasis (52). However, the rate of lymph node detection is very low (53). Depending on serum PSA levels, choline or acetate PET are reported to have a detection rate between 11-75%, and the detection range is 5-44% at PSA <1 ng/mL (54,55,56,57,58,59,60,61). Its main limitation is low sensitivity for micrometastatic disease. Therefore, choline PET/CT is now recommended for patients with biochemical recurrence and PSA >1 ng/mL (29). Ga-68-PSMA-11 PET/CT is promising for determining tumor location in patients with biochemical recurrence. There are studies reporting a high overall accuracy rate of around 54-100% for median PSA levels of 0.2-4.6 ng/mL. Moreover, the detection rate in patients with PSA level <1 ng/mL is between 44-73%. These results are also confirmed by a prospective study including 31 patients. Location of recurrence was accurately determined in 22/31 patients (71%) using Ga-68-PSMA-11 PET/CT (62). In this patient group, median PSA was reported as 2.0 ng/mL (0.1-130 ng/mL). The detection rate was found to be 47.6% in those with PSA <0.83 ng/mL (62). The rate of detection by Ga-68-PSMA-11 PET/CT increased with elevated PSA levels (63-65). However, Gleason score and neoadjuvant or adjuvant androgen therapy did not affect the detection rate (63).

Impact on Patient Management

Ga-68-PSMA-11 PET/CT has resulted in management changes in patients with early biochemical recurrence (65,66). In two different studies, management of treatment was changed in 60% and 29% of patients scheduled for radiotherapy based on the results of Ga-68-PSMA-11 PET/CT (65,66). In one of those studies, Sterzing et al. (66) reported a switch from radiotherapy to systemic treatment in only 4 of 42 patients (10%) and changes in radiation dosage and location only in the other 21 of 42 patients (50%). In the other, Van Leeuwen et al. (65) reported significant management changes in 11/20 patients (55%) who were scheduled for salvage radiotherapy. Of these patients, therapy was changed from radiotherapy to surgery in 1/20 (5%), androgen suppression treatment was added for 6/20 (30%), salvage radiotherapy was changed to extrapelvic stereotactic radiotherapy in 3/20 (15%), and stereotactic radiotherapy was added for an extrapelvic lesion in 1/20 (5%) (65). Overall, evidence to date shows that PSMA imaging has overcome the limitations of choline PET/CT and conventional imaging modalities in patients with biochemical recurrence and low PSA levels. In addition, PSMA imaging influences treatment approach in some patients with biochemical recurrence. Therefore, PSMA imaging has the potential to become routine for patients with biochemical recurrence due to its superiority over conventional imaging modalities and its role in guiding therapeutic management (66).

PSMA Therapy

Current approaches in metastatic castration-resistant prostate cancer include chemotherapy, hormone therapy, and abiraterone or enzalutamide. In addition, Radium-223 was approved for the treatment of symptomatic bone metastases. The first RLT in prostate cancer used Lu-177-J591, a monoclonal antibody with affinity for the extracellular domain of PSMA (67). Although this treatment showed promising outcomes, it was limited due to myelosuppression (67). With the development of PSMA ligands with nanoparticles, Lu-177-based radionuclide therapies are being reinvestigated in patients with metastatic prostate cancer. Some studies have yielded promising results using Lu-177-labeled PSMA ligands. The mean tumor dose is 6-12-fold higher than in the critical organs, kidneys, and salivary glands (68). Moreover, the tumor/organ ratio is higher than Lu-177-DOTATE, which is the standard RLT for NET patients (68,69). Reduction in PSA was observed in 59-89% of patients after a single dose of Lu-177-PSMA RLT using PSMA-617 or PSMA I&T. In addition, the reduction in PSA was greater than 50%

in 26.3-58.9% of the patients. Furthermore, Ga-68-PSMA PET/CT was performed on patients at 6 months after the last cycle to determine disease progression. Based on different criteria, partial treatment response was seen in 56-91%, stable disease in 0-64%, and progression in 9.1-36%. Finally, overall survival was compared in patients under Lu-177-PSMA treatment among a cohort receiving best supportive therapy. It was reported that overall survival was 29.4 weeks with Lu-177-PSMA treatment versus 19.4 weeks with best supportive care (HR: 0.44, 95% CI 0.20-0.95, P=0.031) (70). In conclusion, Lu-177-PSMA can potentially prolong life. A similar effect was shown in advanced prostate cancer using I-131-labeled MIP-1095 compound, but the data are limited (24).

Toxicity

Patients receiving Lu-177-labeled PSMA RLT experienced severe side effects. Mild and reversible side effects noted in retrospective studies included dry mouth, nausea, and fatigue (70,71,72,73,74,75,76). Heck et al. (74) reported grade 1-2 toxicity such as anemia (32%) and thrombocytopenia (25%). In another study, grade 3 anemia occurred in 2/24 patients (8.3%) (72). No marked nephrotoxicity (grade 3,4) was observed (71,72,73,74,75,76). Most patients tolerated therapy, and no acute side effects after Lu-177-PSMA injection have been reported (72,73,74,75,76). Ahmadzadehfar et al. (72) retrospectively studied adverse events in 10 patients and reported grade 3/4 hematological toxicity in 1 patient 7 weeks after RLT administration. Most patients (n=6) showed no hematological toxicity during the 8 weeks after injection (72). When compared with current chemotherapies, Lu-177-based therapies have milder side effects. In the GETUG-AFU 15 study, 38% of patients receiving chemotherapy together with androgen suppression treatment experienced severe side effects, primarily neutropenia (77).

Conclusion

Lu-177-PSMA therapy has shown promising results. It is efficient and well-tolerated, and can prolong overall survival. However, most studies have been retrospective in design. Further randomized, controlled studies are needed to demonstrate the clinical value of PSMA-targeted RLT.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Consept: A.H., Design: D.B., A.H., Data Collection or Processing: D.B., Analysis or Interpretation: A.H., Literature Search: D.B., A.H., Writing: D.B.

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