



Prostate-specific membrane antigen-mediated theragnostics in prostate cancer

Prostate-specific membrane antigen (PSMA), also known as glutamate carboxypeptidase II, is a zinc metalloenzyme encoded by *FOLH1* that resides in the cellular membrane [1]. As noted by its name, PSMA is highly expressed in prostate cancer cells as high as 100 to 1,000 times compared with in normal prostate cells and even higher in advanced stages and castration-resistant prostate cancers (CRPCs). PSMA is also expressed in other organs at low levels, including the brain, kidneys, salivary glands, and intestines and their derivative cancers and neovasculature [2]. Although it is not an exclusive marker of the prostate cell or its malignancies, the expression pattern of PSMA in the prostate paves the way to targeted diagnostic and therapeutic strategies.

The incomparably prominent expression of PSMA in prostate cancers has inspired PSMA ligand-mediated imaging and drug delivery. Several PSMA ligands have been developed that target the extracellular catalytic domain or short intracellular domains. The majority of the PSMA ligands are urea-based inhibitors with high affinity and specificity. PSMA resides on the cellular membrane as a monomer, which upon ligand binding combines to form a homodimer and is then internalized to the cytoplasm or lysosomes. The internalized PSMA allows diagnostic or therapeutic materials to be readily accumulated in prostate cancers [3].

DIAGNOSTIC VALUE OF PROSTATE-SPECIFIC MEMBRANE ANTIGEN LIGANDS

The radiopharmaceutical agent ^{68}Ga -PSMA-HBED-CC was introduced in 2012 and has become the most popular agent for PSMA-PET (positron emission tomography) imaging. HBED-CC, or *N,N'*-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-*N,N'*-diacetic acid, is a ^{68}Ga chelator that binds efficiently at room temperature, thus bestowing the agent with thermodynamic stability. Although the 2020

EAU guidelines recommend cross-sectional abdominopelvic images such as computed tomography or magnetic resonance with bone scan in intermediate or high-risk patients and not ^{68}Ga -PSMA-PET for initial staging, evidence for the benefits of ^{68}Ga -PSMA-PET is growing, with acceptable sensitivity (33%–92%, per lesion) and specificity (82%–100%, per lesion). Accordingly, a prospective study confessed that the use of ^{68}Ga -PSMA-PET for initial staging changed treatment plans in 21% patients with intermediate or high-risk prostate cancer. Moreover, in patients experiencing biochemical recurrence, ^{68}Ga -PSMA-PET is desirable for identifying metastatic lesions with high sensitivity and specificity over conventional modalities. In particular, ^{68}Ga -PSMA-PET can precisely detect distant metastasis when prostate-specific antigen (PSA) levels at biochemical recurrence are lower than 0.5 ng/mL. The influence of the presence of metastatic lesions when determining treatment plans is substantial. In a prospective study, ^{68}Ga -PSMA-PET unveiled metastatic lesions in 80% of patients. In a pooled meta-analysis, 27% to 70% of initially intended treatments for recurrent prostate cancers were changed after ^{68}Ga -PSMA-PET. Conventional salvage radiotherapy, which is blindly delivered to the pelvic cavity and not to identified lesions, was reduced, as was systemic androgen-deprivation therapy (ADT) (more than half from 26% to 12%) [4]. These changes in treatment plans in each patient are in line with the goals of precision medicine to pursue personalized management. In addition, ^{68}Ga -PSMA-PET provides alternative treatment options for identified metastatic lesions, including surgical resection and SBRT, which permits favorable prognosis. Although further study is required, a reduction in ADT when adequate local control can be achieved for identified lesions is also notable for avoiding the adverse effects of unnecessary treatment.

THERAPEUTIC VALUE OF PROSTATE-SPECIFIC MEMBRANE ANTIGEN LIGANDS

The treatment for advanced or metastatic prostate cancer has mainly circled around androgen deprivation, but the cancer develops into CRPC. Second-generation anti-androgen agents such as abiraterone acetate and enzalutamide have shown benefit by inhibiting further signals targeting androgen synthesis or androgen receptor nuclear transportation, but CRPCs eventually evolve to be refractory. In addition, taxane-based chemotherapy such as docetaxel and cabazitaxel benefit only a few months of survival with significant adverse effects. Derived from the sensitive and specific binding property of PSMA ligands to prostate cancers, radioimmunotherapy has emerged for CRPCs.

In radioimmunotherapy, the beta-emitting radioisotope replaces the diagnostic isotope attached to the PSMA ligand, which is readily delivered to the site of metastasis with the aim of *theragnostics*. The PSMA ligand-conjugated radioisotope binds to PSMA, which is highly expressed on prostate cancer cells and even more highly expressed in metastatic CRPCs, and is then internalized immediately. The most widely reviewed PSMA-radioisotope-conjugation, ^{177}Lu -PSMA-617, has shown promising results in mCRPCs by reducing PSA by more than half in 37% of prostate cancer patients, as shown in a systematic meta-analysis of 9 well-designed studies without significant adverse effects. Objective responses on lymph node or visceral metastasis satisfying RECIST 1.1 criteria were reported in 82% of patients [5]. In another study, ^{177}Lu -PSMA-617 therapy decreased PSA more than 50% in 44.2% of patients with CRPC and prolonged overall survival in responders compared with nonresponders. Of note, the treatment response should not be determined after the first cycle of therapy, because as much as one-third of the patients experienced a delayed decline in PSA after additional cycles. Recently, the TheraP (ANZUP 1603) phase 2 trial released remarkable results comparing ^{177}Lu -PSMA-617 with cabazitaxel in mCRPC that had previously been treated with docetaxel and exhibited progression. PSA response, defined as a reduction of more than 50%, was greater for ^{177}Lu -PSMA-617 than for cabazitaxel treatment (66% vs. 37%, $p < 0.0001$). Progression-free survival was also delayed by ^{177}Lu -PSMA-617 over cabazitaxel (hazard ratio: 0.63, $p = 0.0028$). Furthermore, ^{177}Lu -PSMA-617 showed fewer grade 3–4 adverse effects (33% vs. 53%) [6]. These results are reflected in the questionnaire responses from the participants of this trial, which showed improved quality of life and symptoms after ^{177}Lu -PSMA-617, leading to the

participants' preference for it. Remarkably, the ongoing phase 3 VISION trial in patients with mCRPC previously treated with second-generation anti-androgens and taxane-based chemotherapy released its first results at the 2021 ASCO annual meeting. ^{177}Lu -PSMA-617 was reported to have improved radiologic progression-free survival with a hazard ratio of 0.4 and overall survival with a hazard ratio of 0.62 with further favorable results on the objective response rate, disease control rate, and time to first symptomatic skeletal event [7]. In addition, alpha-emitting radioisotope such as ^{213}Bi and ^{225}Ac conjugated with PSMA-617 suggested a favorable response in nonresponders to ^{177}Lu -PSMA-617 treatment [2]. The upcoming results of clinical trials on PSMA-mediated theragnostics will soon change clinical practice.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Seung-hwan Jeong and Cheol Kwak. Data acquisition: Seung-hwan Jeong. Drafting of the manuscript: Seung-hwan Jeong. Critical revision of the manuscript: Cheol Kwak. Obtaining funding: Cheol Kwak. Administrative, technical, or material support: Seung-hwan Jeong. Supervision: Cheol Kwak. Approval of the final manuscript: Seung-hwan Jeong and Cheol Kwak.

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