Why Targeting PSMA Is a Game Changer in the Management of Prostate Cancer

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Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein that is highly expressed on prostate adenocarcinomas, exhibits only limited expression in benign and extraprostatic tissues, and thus represents an ideal target for the diagnosis and management of prostate cancer. Since its discovery over 30 y ago, significant effort has been made to develop clinical technology targeting PSMA. The last 5 y have seen an explosion of development of new agents targeting PSMA for diagnostic and therapeutic use. Imaging agents targeting PSMA have been developed for SPECT and PET platforms. PSMA PET imaging appears to outperform traditional imaging in the high-risk localized-disease state, in patients with biochemical recurrence after treatment, and in advanced disease. To date, most of the reported clinical studies of therapeutic agents have used PSMA-targeted radiometals to deliver β-radiation to metastatic disease sites, with ^{177}Lu being the most widely investigated therapeutic radioisotope. Studies of both antibodies and small-molecule agents have been published and have demonstrated encouraging results. Safety appears generally limited to mild transient bone marrow toxicity and xerostomia because of uptake of the small-molecule agents in the salivary glands. Radiologic responses can be dramatic, and decreases in pain have been observed. The effect on overall survival, however, has yet to be demonstrated.

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Advances in the early detection and treatment of prostate cancer have resulted in a 50% decrease in mortality from prostate cancer in the United States over the last 25 y (*1*). Despite these strides, a subset of men either present with de novo metastatic disease or will progress to the metastatic disease state despite attempts to cure at the localized-disease state. Although androgen deprivation therapy slows disease progression, metastatic tumors ultimately develop castration resistance and are generally incurable. The past decade has seen the development of treatments of various modalities for metastatic castration-resistant prostate cancer (mCRPC), including second-generation endocrine manipulation, cytotoxic chemotherapy, cellular immunotherapy, and ^{223}Ra-dichloride. Although these agents have been shown to prolong overall survival, the benefits conferred are modest, and mCRPC remains a leading cause of cancer death, killing over 300,000 men worldwide annually (*2*).

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BACKGROUND

Prostate-specific membrane antigen (PSMA) is a 750–amino-acid type II transmembrane glycoprotein encoded by the folate hydrolase 1 gene located on the short arm of chromosome 11 (*3*). The name *PSMA* is a misnomer, as the protein is expressed not only on both benign and malignant prostate epithelium but also on a variety of extraprostatic tissues, including the proximal renal tubules (*4*), jejunal brush border (*5*), salivary glands (*5*), and neovasculature of several solid tumors (*6*). Structurally, the transmembrane protein consists of a 19–amino-acid intracellular domain, a 24–amino-acid transmembrane domain, and a large, 707–amino-acid, extracellular domain (*7*).

Histologically, PSMA is detectable at modest levels in the epithelium of benign prostate tissue but demonstrates 100- to 1,000-fold expression on the epithelium of prostate adenocarcinomas (*4,8*). It is expressed in most tumors, and a positive correlation has been observed between higher PSMA expression and various measures of tumor aggressiveness, including Gleason grade (*8*), tumor stage (*9*), biochemical recurrence (*10*), and castration resistance (*11*). The cytoplasmic domain of PSMA contains a motif that results in internalization of bound PSMA via clathrin-coated pits (*12*). This process provides the possibility that PSMA-targeting agents might be internalized and concentrated within tumor cells. PSMA is thus an attractive target for diagnostic and therapeutic targeting for several reasons, including high expression on prostate cancer cells, limited expression on benign prostate tissue, limited expression on nonprostate tissue, an extracellular domain that can be targeted by antibodies, a well-characterized binding site that can be targeted by small-molecule ligands, and a motif that results in internalization of bound agents and concentration within malignant cells.

TARGETING AGENTS

Antibodies

The first steps in targeting PSMA took place in the late 1980s and involved generation of the 7E11-C35 antibody, which is specific to an epitope at the intracellular domain of PSMA (*13*). This antibody was then labeled with ^{111}In, allowing for use with SPECT imaging. This agent, known as capromab pendetide (ProstaScint; Aytu BioScience, Inc.) was Food and Drug Administration–approved in 1996 for the detection of soft-tissue metastases. When ProstaScint was evaluated for use in initial staging, 2 large multicenter trials demonstrated sensitivities of 52%–62% and specificities of 72%–96% using pelvic lymphadenectomy as the truth standard,

outperforming both CT and MRI (*14*). When used for the detection of suspected recurrent or residual cancer after treatment of the primary tumor, ProstaScint demonstrated a sensitivity of 49%–77% and specificity of 35%–71% (*14*). Despite this modestly improved performance compared with traditional imaging, the relatively poor sensitivity of ProstaScint in the setting of low prostate-specific antigen (PSA) levels, difficulties in anatomic localization because of the limitations of SPECT, and significant operator dependence resulted in relatively limited use.

To improve on these limitations, huJ591, a humanized monoclonal IgG1 antibody that binds an extracellular epitope of PSMA, has been developed for use with both γ- and photon-emitting metalloradionuclide agents (*15*). The antibody has been used in several early-phase clinical trials for both imaging and therapy (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org) (*16–19*). Because IgG antibodies are not filtered at the glomerulus and remain within the blood pool for several days, imaging must be performed 6–8 d after infusion to allow clearance of the antibody from the blood pool. An 80-kDa minibody that has been genetically engineered to lack the Fc-receptor domain, known as ^{89}Zr-Df-IAB2M, was synthesized with the aim of generating faster blood clearance in order to allow for imaging at a shorter time interval (*20*). The initial studies suggest that a 48-h wait time between infusion and imaging may still be required.

Small-Molecule PSMA Ligands

Characterization of the active substrate-recognition site of the PSMA molecule has allowed for the development of numerous agents engineered to bind to this site. Small molecules have the theoretic advantage over antibodies of achieving better tumor penetration and faster clearance from the blood pool, allowing for infusion and imaging to be performed during a single patient-visit. Numerous small-molecule agents, labeled with a range of radionuclides for use with both SPECT imaging and PET imaging, as well as for the delivery of radiometallonuclides for treatment purposes, have been developed and are in various stages of clinical use (Table 1 and Supplemental Table 1). Several of the more promising small-molecule agents are discussed below.

^{68}Ga-PSMA-HBED-CC (^{68}Ga-PSMA-11) is the most widely used PET agent for PSMA-targeted imaging. First described in 2012, the agent consists of the HBED-CC chelator to which the ^{68}Ga is bound, a lipophilic linker, and a urea-based Glu-CO-NH-Lys motif that binds to the active site of the PSMA molecule (*21*). It displays low-level natural uptake in the kidneys, salivary glands, lacrimal glands, liver, spleen, and bowel and has demonstrated the ability to detect prostate cancer within the prostate gland, within small nodal metastases, within bony lesions, and even within more widespread dedifferentiated tumors (*22–24*). Because the agent is filtered at the glomerulus, high levels of activity are present in the urine, potentially making the detection of local recurrences more difficult; however, nodal metastases near the bladder have been detected (*24*). A systematic review was published in 2016 by Perera et al. evaluating the sensitivity and specificity of ^{68}G-PSMA-HBED-CC in various clinical settings (*25*). Further details of the agent's performance will be discussed below.

Another area of robust investigation in PSMA ligands involves agents that use ^{18}F, a radionuclide that has several theoretic advantages over ^{68}Ga, including better image resolution because of a shorter positron range and a higher positron yield. Like the ^{68}Ga agents, ^{18}F agents can be infused and imaged at the same visit. The first of these agents to be tested clinically was ^{18}F-DCFBC, which has been evaluated both for disease assessment within the gland (*26*) and for detection of metastases (*27,28*). Although initial results were encouraging, the significant blood-pool activity of the agent prompted efforts to refine it and improve its performance. The result of these efforts was a second-generation agent, 2-(3-(1-carboxy-5-[(6-^{18}F-fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid (^{18}F-DCFPyL), which was initially evaluated in a cohort of 9 patients with metastatic disease (*29,30*). As hoped, the agent demonstrated a marked improvement in maximum tumor–to–blood-pool uptake ratios (*30*), allowing for improved visual conspicuity of suspected disease. Another agent, ^{18}F-PSMA-1007, is also in development and has shown the ability to detect micrometastases (*31*) in the biochemical recurrence setting.

NOTEWORTHY

- PSMA has been a molecular target of interest in prostate cancer since its discovery in 1986.
- A variety of antibodies and small-molecule imaging agents targeting PSMA have demonstrated excellent early results for a variety of disease states.
- Radioimmunotherapeutic and radioligand agents are currently being investigated for use in the mCRPC setting, with several demonstrating encouraging clinical responses.
- The effect of these agents on overall survival remains a subject of investigation.

DIAGNOSTIC TARGETING

High-Risk Initial Diagnosis

At least 4 published studies have evaluated the performance of PSMA-targeted agents for use in initial staging of intermediate- and high-risk disease for which histopathologic correlation was performed (*32–35*). These studies used the ^{68}Ga-PSMA-HBED-CC tracer, and in all 4 studies, PET with this tracer outperformed traditional CT or MRI for lymph node staging, with both improved sensitivity and improved specificity on both a per-patient and a per-template basis. On a per-patient basis, sensitivities ranged from 33% to 91% and specificities from 67% to 100%. On a per-template basis, sensitivities ranged from 74% to 86% and specificities from 88% to 99%.

Biochemical Recurrence

At present, biochemical recurrence can be detected long before imaging technology allows anatomic localization of disease. This provides challenges for management because local radiotherapy, which is known to prolong both disease-free and overall survival (*36*), is most effective when applied at low PSA levels, although local recurrence presently can only be inferred from pathologic data and PSA kinetics. Given reticence to proceed with local salvage radiotherapy without definitive evidence of local recurrence, imaging technology to improve the localization of disease recurrence is of paramount interest and represents one of the most robust areas of PSMA-targeted imaging research. Afshar-Oromieh et al. published the largest study for this indication, an analysis of 1,007 men with biochemically recurrent disease (*22*) who underwent PET using the ^{68}G-PSMA-HBED-CC tracer. In 79.5% of patients, at least 1 lesion suggestive of prostate cancer was identified, including lesions in bone, soft tissue, and viscera. There was

TABLE 1
Key Reports of PSMA-Targeted Antibody and Small-Molecule Radioligand Therapy for mCRPC

First author	PMID	Report date	Agent	*n*	Key efficacy outcomes	Key safety outcomes
Bräuer	28624848	September 2017	^{177}Lu-PSMA-617	59	↓PSA in 91% of pts; ≥50% ↓PSA in 53%; median OS 32 wk; PSA decrease after 1 cycle and AP <220 U/L associated with longer OS	2 pts each with grade 3 leukopenia and thrombocytopenia; 12 with new-onset xerostomia
Ahmadzadehfar	28488028	August 2017	^{177}Lu-PSMA-617	52	After 1 cycle, ↓PSA in 81% of pts and ≥50% ↓PSA in 44%; 50% of cycle 1 NRs with no response to subsequent treatment; survival of cycle 1 Rs more than twice that of cycle 1 NRs (68 vs. 33 wk)	Not reported
Afshar-Oromieh	28280855	June 2017	^{131}I-MIP-1095	34	≥50% ↓PSA in 70.6% of pts; first dose most effective; no association between applied activity and PSA response; median OS 17 mo	Measurable leukopenia and thrombocytopenia, significant xerostomia transient but worsening with increasing number of treatments
Kratochwil	28408529	April 2017	^{225}Ac-PSMA-617	14	At 100 kBq/kg, duration of ↓PSA <4 mo; antitumor effects additive if therapy repeated every 2 mo	Severe xerostomia: dose-limiting toxicity at >100 kBq/kg
Rahbar	27765862	January 2017	^{177}Lu-PSMA-617	145	↓PSA in 60% of pts; ≥50% ↓PSA in 45%; elevated AP and visceral metastases negative predictors of response	10%, 4%, and 3% of pts with anemia, thrombocytopenia, and leukopenia, respectively; 8% with xerostomia
Fendler	27683041	January 2017	^{177}Lu-PSMA-617	15	2 cycles of 3.7 GBq (n = 5) or 6.0 GBq (n = 10); ↓PSA in 80% of pts; 67% with PR or SD; pain relief in 70% of symptomatic pts	3 pts with grade 3 events (nausea, leukopenia, anemia)
Kratochwil	26985056	August 2016	^{177}Lu-PSMA-617	30	↓PSA in 70% of pts; ≥50% ↓PSA in 43%; PSA response >24 wk in 8/11 pts receiving 3 cycles	9 pts with worsening of anemia; 8 with leukopenia; 6 with thrombocytopenia
Baum	26795286	January 2016	^{177}Lu-PSMA-I&T	56	↓PSA in 80.4% of pts; ≥50% ↓PSA in 58.9%; 72% PR or SD by CT; 64% PR or SD by ^{68}Ga-PSMA PET	2 pts with transient xerostomia; statistically significant/clinically insignificant decreases in leukocyte and erythrocyte counts
Tagawa	23714732	September 2013	^{177}Lu-huJ591 mAb	47	↓PSA in 59.6%; ≥50% ↓PSA in 10.6%	Grade 4 thrombocytopenia in 46.8%; grade 4 neutropenia in 25.5%
Milowsky	15173215	July 2004	^{90}Y-huJ591 mAb	29	↓PSA of 85% and 70% in 2 pts; 6 pts with SD	2 pts with thrombocytopenia and non–life-threatening bleeding

pts = patients; AP = alkaline phosphatase; NRs = nonresponders; Rs = responders; mAb = monoclonal antibody; PMID = PubMed identification number; OS = overall survival; PR = partial response; SD = stable disease.

a clear relationship between the likelihood of a positive scan result and PSA level: a 46% likelihood at a level of 0.5 ng/mL or less, 73% at 0.51–1.0 ng/mL, 80% at 1.1–2.0 ng/mL, 86% at 2.1–3.0 ng/mL, 91% at 3.1–5.0 ng/mL, 94% at 5.1–7.0 ng/mL, 91% at 7.1–10 ng/mL, and 96% at more than 10 ng/mL. A multivariable logistic regression analysis found that log PSA and receipt of androgen deprivation therapy predicted a positive scan result but that Gleason score did not. These results are generally consistent with a report from Eiber et al., who published on a cohort of 248 consecutive patients with biochemical recurrence after radical prostatectomy. PSMA PET is especially relevant at low PSA values given that guidelines for salvage radiotherapy recommend treatment at a PSA level of less than 0.5 and that other PET tracers, such as ^{18}F-choline, demonstrated limited sensitivity at this level (19%–36%). Apropos to this point, Bluemel et al. published a report on 125 patients with biochemical recurrence after radiation or radical prostatectomy who underwent ^{18}F-choline PET and, if negative, ^{68}G-PSMA–imaging and therapy (I&T) PET/CT (^{177}Lu-DOTAGA) (*37*). These investigators found that ^{68}G-PSMA-I&T detected sites of BCR in 44% of patients with a negative ^{18}F-choline PET/CT result (*37*), with the incremental benefit of the PSMA study being most pronounced in the subset of patients with a PSA level of less than 1 ng/mL.

Metastatic

Most published studies have demonstrated that PSMA-targeting agents, both antibody-based and small-molecule ligands, are safe and provide high sensitivity and specificity for staging lymph node, soft-tissue, and bony metastases (*20,27,29,30,38–41*). One study, by Rowe et al.—a head-to-head comparison of the performance of conventional imaging versus ^{18}F-DCFPyL—demonstrated some of the key considerations in this area (*30*). First, ^{18}F-DCFPyL detected over 3 times the number of metastatic lesions detected by conventional imaging. Second, the authors discussed the ability of ^{18}F-DCFPyL to detect metastases in small lymph nodes, noting the failure of simple size cutoff to distinguish between benign and malignant nodes. Finally, ^{18}F-DCFPyL detected metastatic disease in the periprostatic soft tissues, an area difficult to assess with either CT or MRI, and the authors highlighted a case in which a patient with normal results on pelvic MRI showed a perirectal metastasis on ^{18}F-DCFPyL PET. The main limitation of this study and others in this area is the lack of a systematic formal histologic evaluation on a lesion-by-lesion basis to serve as the truth standard. As such, the true performance of PSMA-targeted imaging for metastatic disease remains incompletely evaluated. Nevertheless, the initial studies provide strong preliminary evidence that PSMA-targeted imaging agents are likely to outperform traditional imaging procedures for the detection of metastatic disease. The value of molecular imaging to monitor therapy is, at present, unproven with respect to overall survival. Unfortunately, molecular imaging is not included in ongoing large trials on advanced disease.

THERAPEUTIC TARGETING

Targeted cancer therapy aims to achieve sensitive and specific on-target, on-tumor cell death while sparing normal tissues. Great effort has been made to develop agents that target PSMA for treatment in the mCRPC disease state, with the appreciation that prostate cancer is radiosensitive, prompting investigation into the use of radiopharmaceuticals as potential candidate effector agents. Most published studies on nascent radiopharmaceuticals describe small-molecule agents that use ^{177}Lu as the radiometal, but early-phase studies have evaluated antibody-based therapies as well. A summary of the key published reports is provided in Table 1. Several notable agents are discussed below. No randomized studies exist to date.

The first PSMA-targeted radioimmunotherapeutic studies used the huJ591 antibody. Two phase 1 dose-finding studies, one using ^{90}Y and one using ^{177}Lu, were published (*18,19*), followed by a phase 2 study using ^{177}Lu and published in 2013 by Tagawa et al. (*17*). In the latter, 47 patients were treated at 2 doses (2,405 and 2,590 MBq/m^2). Key outcomes included a PSA decline of at least 50% in 10.6% of patients and a PSA decline of any amount in 59.6% of patients. Median overall survival for the entire cohort was 17.6 mo, with higher-dose patients surviving almost twice as long (21.8 vs. 11.9 mo). Myelosuppression was the main observed side effect, including grade 4 thrombocytopenia in almost half the patients, but was reversible. No significant hemorrhages occurred.

More recent attention has been focused on small-molecule PSMA-targeting radioligand therapies, many of which use theranostic agents. Theranostic agents are those in which the chelator is capable of binding radiometals for both imaging (^{68}Ga) and treatment (^{177}Lu). Like imaging agents, small-molecule radioligand agents have the advantage of clearing from the blood more quickly than antibodies, resulting in lower doses of radiation delivered to normal tissues.

The best-studied PSMA-targeted radioligand therapeutic agent is ^{177}Lu-PSMA-617. The first reported cohort was published in 2015 (*42*), and since that time multiple investigator groups have published results evaluating this agent (*43–46*). The largest study to date is a retrospective multicenter cohort of 145 patients from 12 centers across Germany (*47*). Some variation in efficacy outcomes is seen across the studies: after a single treatment, 59%–79% of patients experienced a PSA decrease, with 32%–45% of patients experiencing a decrease of at least 50%. The studies by Rahbar et al. (*47*) and Kratochwil et al. (*43*) suggested that patients who receive multiple treatments continue to respond to subsequent treatments at a similar, if not increasing, rate. The large German multicenter study demonstrated that the presence of visceral metastases and an alkaline phosphatase level of at least 220 U/L predicted a lower rate of treatment response. The study by Ahmadzadehfar et al. found that responders to the initial cycle of treatment survived over twice as long as nonresponders (*45*). In all cohorts, leukopenia and thrombocytopenia were reported but were mild. Xerostomia was seen but was mild and transient and rarely required salivary replacement.

^{177}Lu-PSMA-I&T is yet another PSMA-targeted radioligand therapeutic agent with early promising results. Baum et al. reported on a group of 56 patients with mCRPC who underwent multiple treatments (*48*). Overall, 80% of patients had a PSA decrease, with 59% having a decrease of more than 50%. Again, mild, self-limited xerostomia was noted in 2 patients, with clinically insignificant decreases in leukocyte and erythrocyte counts. RECIST morphologic response assessment by CT demonstrated a partial response in 20%, stable disease in 53%, and progressive disease in 28%, whereas response assessment by ^{68}G-PSMA PET demonstrated a partial response in 56%, stable disease in 8%, and progressive disease in 36%. The authors pointed out that changes detectable by SUVs on PET/CT may occur before changes in lesion or lymph node size and might be responsible for the discrepancy in response rates.

The PSMA-617 agent has also been tested in early clinical trials with the α-emitting radiometal ^{225}Ac in an attempt to reduce potential hematologic and salivary toxicities (because of the shorter range of α-particles) and potentially to break through radioresistance to ^{225}Lu. In a 14-patient dose-finding cohort, Kratochwil et al. determined that a dose of 100 kBq/kg was the maximum tolerable and that a schedule of dosing every 2 mo appeared feasible (*49*). Efficacy was suggested, and plans for further study are in progress.

Although dramatic radiologic responses have been noted in many of these early-phase PSMA-targeting radioligand and radioimmunotherapeutic trials, and results suggest a role for these agents in the management of mCRPC, there is, at present, no level 1 evidence demonstrating a benefit to overall survival. The impact of cotargeting approaches that create synthetic lethality from DNA damage with poly(ADP-ribose) polymerase inhibitors, next-generation androgen ablation, and platinum-based chemotherapies has not yet been explored.

CONCLUSION

PSMA is a promising molecular target in prostate cancer management for several reasons, including high levels of expression on most prostate cancer cells with limited expression on benign tissues, proven in vivo safety and feasibility in targeting PSMA using antibodies and small molecules, and a motif that provides for internalization and concentration of agents. Several studies have shown that the PET-based imaging assays outperform standard imaging techniques and that these assays appear poised to become a new standard in prostate cancer imaging. Early-phase therapeutic trials of unsealed radiometals have produced promising results in mCRPC; however, more study will be required to prove their effect on meaningful endpoints. PSMA targeting is likely to play a central role in prostate cancer management in the future.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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