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^{225}Actinium-labeled prostate-specific membrane antigen targeting peptide induces complete response in a metastatic prostate cancer patient

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Abstract

Targeted radionuclide therapy has emerged as a promising and potentially curative strategy for high-grade prostate cancer. However, limited data are available on efficacy, quality of life, and pretherapeutic biomarkers. Here, we highlight the case of a patient with prostate-specific membrane antigen (PSMA)-positive metastatic castrate-resistant prostate cancer who displayed complete response to ^{225}Ac-PSMA-617 after having been resistant to standard-of-care therapy, then initially partially responsive but later resistant to subsequent immunotherapy, and resistant to successive ^{177}Lu-PSMA-617. In addition, the patient's baseline germline mutation likely predisposed him to more aggressive disease.

Keywords

^{225}Ac-PSMA, metastatic prostate cancer, radioligand therapy, genetic alterations

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Introduction

Targeted radionuclide therapy (TRT) has emerged as a promising and potentially curative strategy for high-grade prostate cancer (Gleason score 8–10). Targeted radionuclide delivery is achieved via administration of a radiolabeled small molecule that selectively binds to prostate-specific membrane antigen (PSMA), a receptor that is commonly overexpressed in metastatic prostate cancer. TRT with medium-energy β-emitter lutetium-177 (^{177}Lu) conjugated to the human PSMA- targeting ligand PSMA-617 (^{177}Lu-PSMA-617) has shown favorable response rates in heavily pre-treated patients with PSMA-positive metastatic castrate-resistant prostate cancer (mCRPC). Despite these promising results, approximately 30% of patients do not respond to ^{177}Lu-PSMA-617 or are contraindicated due to diffuse red marrow infiltration of mCRPC.[1,2]

Alpha-particle emitting radionuclides (e.g., bismuth-213 (^{213}Bi) and actinium-225 (^{225}Ac)) have been shown to overcome radio-resistance to β-emitters, while concurrently demonstrating more favorable hematologic toxicity profiles than β-emitters.[3,4] In a recent clinical trial, ^{225}Ac-PSMA-617-based TRT induced a $>$ 90% decline in prostate-specific antigen (PSA) serum levels in 82% of chemotherapy-naïve mCRPC patients, of whom 41% demonstrated undetectable serum PSA and remained in remission for 12 months post-TRT.[4] Here, we report a case of complete response to ^{225}Ac-PSMA-617 in a 72-year-old man with mCRPC who had been resistant to standard-of-care therapy, then initially partially responsive but later resistant to

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subsequent immunotherapy, and resistant to successive ^{177}Lu-PSMA-617.

Case report

This is the case of a 72-year-old man with stage IV castrate-resistant prostate cancer. His initial diagnosis was in 2009 with a Gleason score of 4 + 3=7 and no distant metastasis at that time. He underwent prostate pelvic radiation therapy with 69 Gy/27 fractions in 2009; he did not undergo prostatectomy but six years later, in 2015, he underwent bilateral orchiectomies. Due to a rising PSA level of 4.8 ng/mL in 2017, ^{68}Ga (Galllium) PSMA and ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) imaging was performed, demonstrating biopsy-proven PSMA-avid recurrent disease in the prostate gland invading the rectum and bladder, with extension to the left pelvic sidewall. PET/CT imaging also demonstrated biopsy-proven PSMA-avid (FDG non-avid) right sacral metastasis. Foundation One results from the prostate biopsy revealed the following genetic alterations: ATM R1898*, KDM5A R1261W, MLL3 S2117fs*26, MSH2 I454fs*5, SPOP F133L, TP53 R248Q, R273C, PTCH1 K418fs*14. The patient's tumor microsatellite status was revealed to be MSI-HIGH and tumor mutation burden was TMB-High (67 mutations/megabyte).

Due to progression of disease, the patient received docetaxel for six weeks in June 2017 and then continued on Yervoy® (Ipilimumab) + Opdivo® (Nivolumab) for approximately one year. Due to a rectovesicular fistula with perforation, he underwent a left upper quadrant colostomy without complication in August 2017. In September 2017, he had left hydronephrosis due to an existing pelvic mass, and bilateral nephrostomy tubes were placed. Despite initial partial response (resolution of previously seen PSMA-avid, biopsy-proven sacral metastasis and resolution of previously seen PSMA-avid, left pelvic side wall disease), his disease progressed demonstrating a new extension of the tumor in the perineal region as well as invasion into the penile shaft. Repeat biopsy was performed, revealing new AR T878A, AKT1 W80R, TSC2 R751*, splice site 3814 + 2T>C, ATR R223fs*1, DICER1 S1473fs*17, DNMT3A P59fs*13 genetic alterations from the progressed tumoral region with tumor microsatellite status of MSI-HIGH and tumor mutation burden of Tumor Mutation Burden (TMB)-High (98 mutations/megabyte). Immunotherapy was stopped.

The patient then received a total of three cycles of treatment with ^{177}Lu-PSMA from November 2017 through April 2018. He experienced several complications during this period including several right groin/abdominal wall abscesses, mostly due to vesicopubical fistula formation with drainage and posterior spinal fixation due to degenerative collapsed vertebra. Having progressed after the last ^{177}Lu-PSMA treatment, nivolumab was restarted in September 2018. He then underwent urinary diversion with an ileal conduit in December 2018 due to hydronephrosis and repeated events of abscess formations. His disease continued to progress, with new pelvic adenopathy, scrotal subcutaneous nodules, and increased extension into the penis as well as the perineal region. All disease sites and metastatic lesions were proved to be PSMA-avid with ^{68}Ga PSMA positron emission tomography/magnetic resonance imaging (PET/MRI).

Then, in March 2019, when when his PSA level was 33.2 ng/mL before treatment, the decision was made to initiate local control with concurrent low dose pelvic radiation followed by 9.3 MBq ^{225}Ac-PSMA. A second 7.8 MBq ^{225}Ac-PSMA was administered in May 2019, when his PSA level was 1.2 ng/mL. Mild xerostomia was the primary side effect, but no severe hematologic toxicity was observed after TRT. After almost one year of treatment, he exhibited dramatic, complete response with non-detectable PSA.

During follow-up, however, the patient was found to have developed pancytopenia. Thus, a bone marrow biopsy was performed at the end of September 2019, with the following results: CD34 15%–18%, CD117 15–20%, and myeloperoxidase (MPO) 65%. The patient was diagnosed as being between refractory anemia with excess blasts (RAEB)-II and acute myeloid leukemia (AML). He was treated with Vidaza® (Azacitidine) (one cycle) but continued to show severe pancytopenia. Repeat bone marrow aspiration showed persistent high blasts. The decision was made to add Venclexta® (Venetoclax). The patient completed one cycle with red blood cell and platelet transfutions before developing sudden respiratory distress syndrome. Chest CT showed multifocal patchy ground-glass opacities and consolidations. Based solely on the imaging findings and symptoms, it was suspected that the patient had SARS-CoV-2 pneumonia. Despite appropriate management (aggressive steroid regiment, prophylactic intravenous antibiotics), fever and bilateral pulmonary infiltrates persisted without improvement; the patient was then transferred to the intensive care unit due to a new episode of shortness of breath with severe hypoxemia. In spite of intensive supportive therapy, the patient had a refractory hypoxic respiratory failure and died at the end of February 2020. An autopsy was not performed. At the time of his death, his PSA level was 0.03 ng/mL.

Imaging findings

Cross-sectional MR images demonstrating radiologic response as assessed by the change in tumor size after different treatment options are shown in Fig. 1.

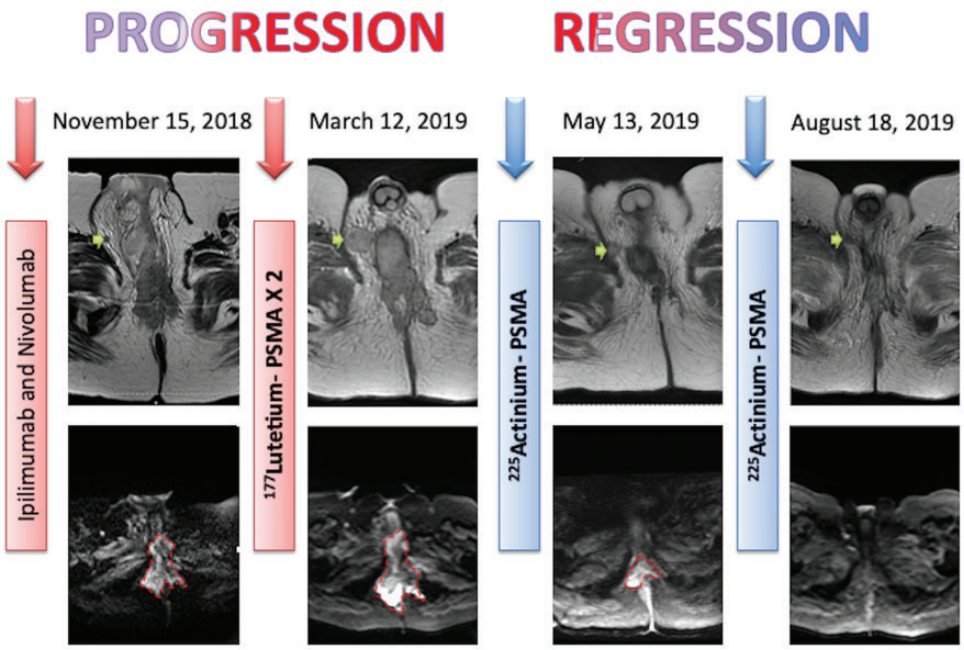

Fig. 1. Cross-sectional magnetic resonance images demonstrating radiologic response as assessed by the change in tumor size after different treatment options. The top row shows selected axial T2-weighted images and the bottom row shows corresponding diffusion-weighted images of the metastatic tumor involving the penis and perineal region (dashed red circle) and right scrotal subcutaneous nodule (green arrow). After the second ^{225}Ac-PSMA treatment, there was no measurable disease at the penis and perineal region and punctate residual right scrotal subcutaneous nodule.

The top row shows selected axial T2-weighted images and the bottom row shows corresponding diffusion-weighted images of the metastatic tumor involving the penis and perineal region (dashed red circle) and right scrotal subcutaneous nodule (green arrow). After the second ^{225}Ac-PSMA treatment, there was no measurable disease at the penis and perineal region and punctate residual right scrotal subcutaneous nodule.

Restaging ^{68}Ga-PSMA PET/ CT images from September 2018, before immunotherapy and ^{177}Lu-PSMA treatments, are shown in Fig. 2. These images show increased uptake in the pelvis, which represented metastatic disease and which was better delineated on the MR images. No other sites of disease were noted elsewhere. Bilateral percutaneous nephrostomy tubes were incidentally noted.

Discussion

High long-term survival rates are associated with localized prostate cancer; metastatic disease is the leading cause of prostate-cancer-associated deaths. For patients with hormone-sensitive metastatic prostate carcinoma, the typical treatment is androgen deprivation therapy (ADT).[5] Most patients initially show clinical response to ADT, but even when castrate testosterone levels are achieved with ADT, disease progression may still take place, resulting in deadly castrate-resistant disease. For patients with mCRPC, available therapies that have shown some survival benefits include chemotherapy with docetaxel or cabazitaxel or with androgen-receptor or androgen-receptor signaling inhibitors (abiraterone and enzalutamide); immunotherapy with checkpoint inhibitors (nivolumab, ipilimumab); and radionuclide treatment (^{177}Lu-PSMA or ^{225}Ac-PSMA).[6,7]

Increased overall survival and long-term responses in multiple disease sites have been shown for immunotherapy with immune check point inhibitors (ICIs).[8] Increased immune cell infiltrate, elevated PD-L1, and high TMB or neoantigens in immunologically "hot tumors" tend to have a better response to immunotherapy.[9] Prostate cancer, however, has been demonstrated to be a "cold tumor" due to minimally invaded immune cells.[10] Thus, multiple prospective trials using ICIs in metastatic prostate cancer have been associated with low response rates, with benefits in only a minority of patients.[11,12]

TMB is an emerging, independent biomarker of outcomes with immunotherapy in multiple tumor types, including prostate cancer.[13] However, metastatic prostate cancer generally has a low TMB (median, 2.9 mutations/megabyte), and only 3.0%–8.3% of advanced prostate cancer tumors have a high TMB.[14,15] In the CheckMate 650 trial, treatment with ICIs (ipilimumab and nivolumab) resulted in an objective response rate of

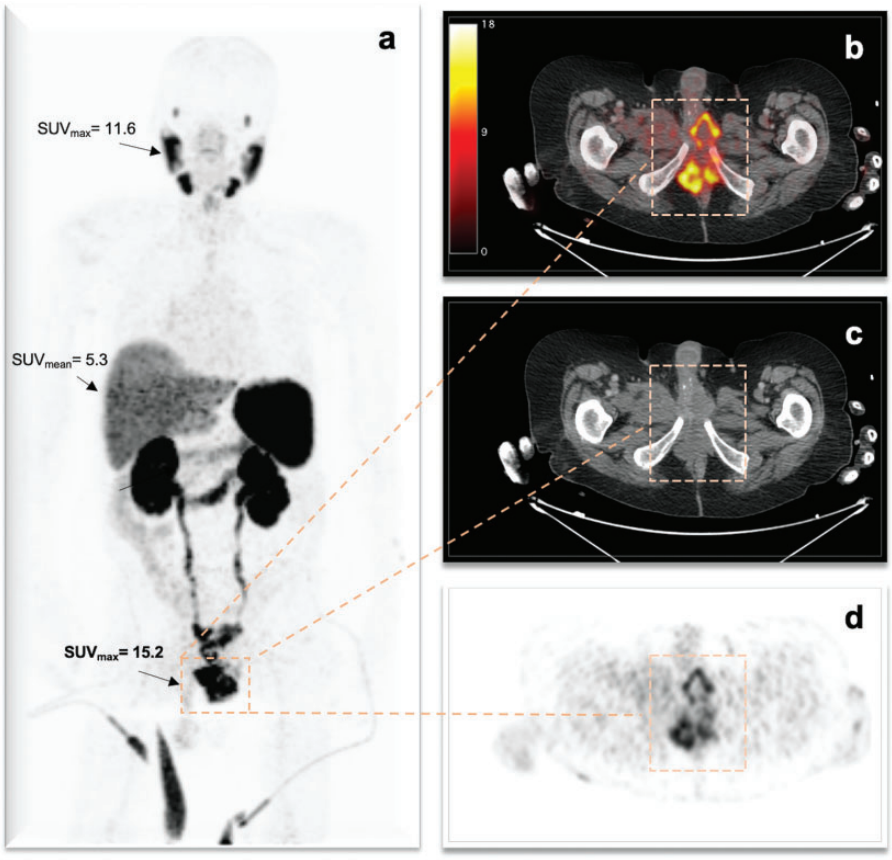

Fig. 2. Restaging ^{68}Ga-prostate-specific membrane antigen (PSMA) positron-emission-tomography (PET)/computed tomography (CT) images from September 2018, before immunotherapy and ^{177}Lu-PSMA treatments. ^{68}Ga-PSMA PET/CT images (3D MIP (a); axial fused PET/CT (b); axial CT (c); and axial PET (d)) showed increased uptake in the pelvis representing metastatic disease (with dotted rectangle) which was better delineated on the MR images. No other sites of disease were noted. Bilateral percutaneous nephrostomy tubes were incidentally noted.

56.3% in patients with a TMB above the median (74.5 mutations/patient); patients with a TMB above the median also had longer radiographic progression-free survival when compared with those with a TMB below the median (7.4 months [95% CI, 6.5 months to not estimated] vs. 2.4 months [95% CI, 1.8–3.9 months], $p < 0.0001$).[16] In this case study, the patient had partial response to ICIs but later had progression of disease, developing multiple new genetic alterations in the tumor genome and microenvironment, probably leading to acquired resistance to ICIs.

PSMA, also known as glutamate carboxypeptidase II or folate hydrolase I, is a transmembrane protein with a large extracellular domain that is easily accessible for binding of ligands.[7] PSMA-based TRT has been shown in several studies to be an efficient and well-tolerated option in patients with mCRPC who relapse after clinically approved treatments of mCRPC or who are ineligible for these treatments.[17,18] ^{177}Lu-PSMA-based TRT has shown considerable therapeutic response as assessed by both serum PSA levels and radiologic imaging findings, but approximately 30% of patients were not responsive; for these patients, dose escalation is severely limited by chronic hematological toxicity.[19,20] Therefore, alternative treatment options are needed for patients such as these who are unresponsive to ^{177}Lu-PSMA-based TRT or who are not suited for the recommended agents. In addition, many patients who respond to ^{177}Lu-PSMA-based TRT will eventually progress.[21] Recently, ^{225}Ac-PSMA-based TRT has shown a $\geq$ 90% decline in serum PSA levels in 82% of 17 chemotherapy-naive patients, and, notably, 41% of these patients remained in remission 12 months after therapy.[4]

In conclusion, in this case study, the patient's baseline germline mutation likely predisposed him to more aggressive disease, and he was resistant to not only ICIs but also ^{177}Lu-PSMA-617. However, he showed significant serum PSA and radiologic response with ^{225}Ac-PSMA-617. We elected not to pursue other therapies targeting molecular alterations in his tumor because of the previously demonstrated survival benefit

of ^{225}Ac-PSMA-617 in men with advanced prostate cancer; however, therapies targeting his tumor's molecular alterations remain as options in the future in similar cases. In summary, ^{225}Ac-PSMA could be an alternative TRT option in patients with mCRPC who have failed or who are ineligible for ^{177}LuPSMA or ICIs.

Declaration of Conflicting Interests

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Informed Consent

Written informed consent was obtained from the patient's guardian for the publication of this case report and the accompanying images.

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