case report

Exceptional Response to ^{177}Lutetium Prostate-Specific Membrane Antigen in Prostate Cancer Harboring DNA Repair Defects

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INTRODUCTION

Prostate-specific membrane antigen (PSMA) is a cell surface protein that is often overexpressed on prostate cancer cells. PSMA-targeted small molecules bound to ^{177}Lutetium (^{177}Lu), a medium-energy B-emitter, have been administered as a targeted therapy for metastatic prostate cancer; the PSMA-targeted small molecule binds to PSMA on the cancer cell surface and is internalized, leading to delivery of a potent but targeted dose of radiation to the cell. A small molecule commonly used for this purpose is PSMA-617, a human PSMA-targeting ligand that can be conjugated to ^{177}Lu. ^{177}LuPSMA-617 therapy has shown great promise in early-phase trials, with a prostate-specific antigen (PSA) response rate of 57% in a phase II prospective study,[1] and randomized trials are currently recruiting internationally. De novo and acquired resistance are common, however, and biomarkers are needed to guide patient selection and rationalize combinatorial approaches.

^{177}LuPSMA-617 induces cell death through double-strand DNA breaks.[2] Mechanisms to repair double-strand DNA breaks are deficient or absent in cells with mutations in homologous repair genes such as *BRCA1* or *BRCA2*, and such mutations are increasingly recognized in metastatic castration-resistant prostate cancer (mCRPC).[3,4] Thus, a deficiency in homologous repair may render a tumor more sensitive to ^{177}LuPSMA-617 and be relevant in CRPC. We report a case of an exceptional response to ^{177}LuPSMA-617 in a 75-year-old man with mCRPC resistant to all standard of care therapies and discuss the mutations that may have driven his response.

CASE REPORT

A 61-year-old man underwent a radical prostatectomy for Gleason 8 prostate cancer 13 years ago. Pathology revealed a multifocal prostate adenocarcinoma with prostatic intraepithelial neoplasia in addition to perineural and perivascular infiltration. There was extensive extraprostatic extension, a focally positive margin, and left-sided seminal vesicle involvement. Postoperative radiotherapy was withheld because of a history of colorectal carcinoma treated with surgical resection followed by adjuvant radiotherapy 25 years prior. Soon after his radical prostatectomy, he biochemically relapsed and was treated with intermittent androgen deprivation therapy. He continued androgen deprivation therapy with introduction and withdrawal of bicalutamide followed by nilutamide. He eventually developed overt metastatic disease, with a perihilar mass found on a computed tomography (CT) scan of the chest, abdomen, and pelvis after 10 years of hormone manipulation. A nuclear medicine bone scan was negative, but an ^{18}F-labeled fluorodeoxyglucose positron emission tomography (PET) scan showed low-grade uptake in the mass, which was confirmed to be metastatic prostate cancer on biopsy. A choline PET was undertaken to assess the extent of his disease and revealed uptake in his left hilar nodes with infiltration in the lingula and involvement of right paratracheal nodes.

Given the extent of disease across both hemithoraces, he commenced enzalutamide. His PSA continued to increase (Fig 1) despite 8 weeks of treatment, and additional radiologic progression with impending bronchial obstruction prompted radiotherapy to his hilar disease. His PSA initially decreased after radiotherapy but began to increase soon after. Restaging CT scan of the chest, abdomen, and pelvis after radiotherapy revealed new liver metastases. A biopsy to exclude small-cell transformation was nondiagnostic. He was initiated on docetaxel chemotherapy but experienced disease progression through three cycles of treatment, with an ongoing PSA increase and radiologic progression on CT scan. He then received two cycles of cabazitaxel, after which a restaging CT scan showed enlargement of his liver metastases and development of new pelvic nodal metastases.

Having progressed through all standard lines of therapy, this patient was enrolled in a clinical trial of ^{177}LuPSMA-617 therapy and received 4 × 6.5 gigabecquerel doses once every 6 weeks (ANZCTR identifier: ACTRN12615000912583). His PSA decreased from 325 μg/L at baseline to a nadir of 1.57 4 months after his final cycle of treatment (Fig 1). He achieved a partial response at all sites of disease on ^{68}Ga-PSMA PET and CT imaging (Fig 2) and clinically improved, with resolution of his anorexia, fatigue, and right upper quadrant abdominal pain.

Seven months after his last cycle of ^{177}LuPSMA-617, his PSA increased sharply to 114 μg/L associated with

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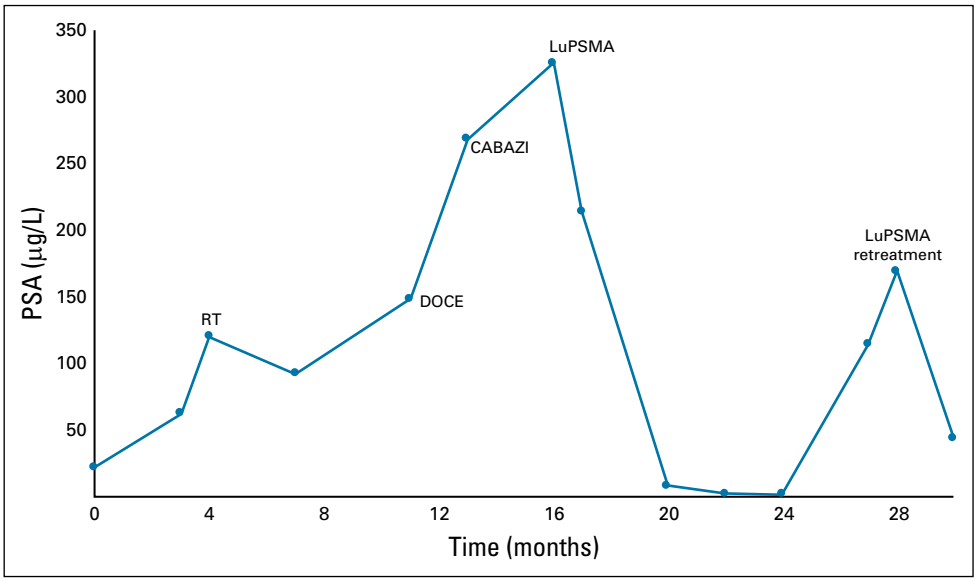

FIG 1. Plot of prostate-specific antigen (PSA) values over time. Treatment regimens: CABAZI, cabazitaxel; DOCE, docetaxel; ENZ, enzalutamide; LuPSMA, ^{177}Lutetium prostate-specific membrane antigen; RT, radiotherapy.

the return of his right upper quadrant abdominal pain. He was consented for prescreening of his circulating tumor DNA (ctDNA) for a poly ADP-ribose polymerase (PARP) inhibitor trial, but while awaiting this result, his pain increased significantly, with derangement of his liver function tests and a further increase in his PSA. He was approved for an additional two compassionate 7.0-gigabecquerel doses of ^{177}LuPSMA-617; he received these with clinical and radiologic responses associated with a PSA response from 169 to 43 after the first dose.

A Resolution Bioscience targeted ctDNA analysis for DNA repair defects revealed abnormalities in three homologous

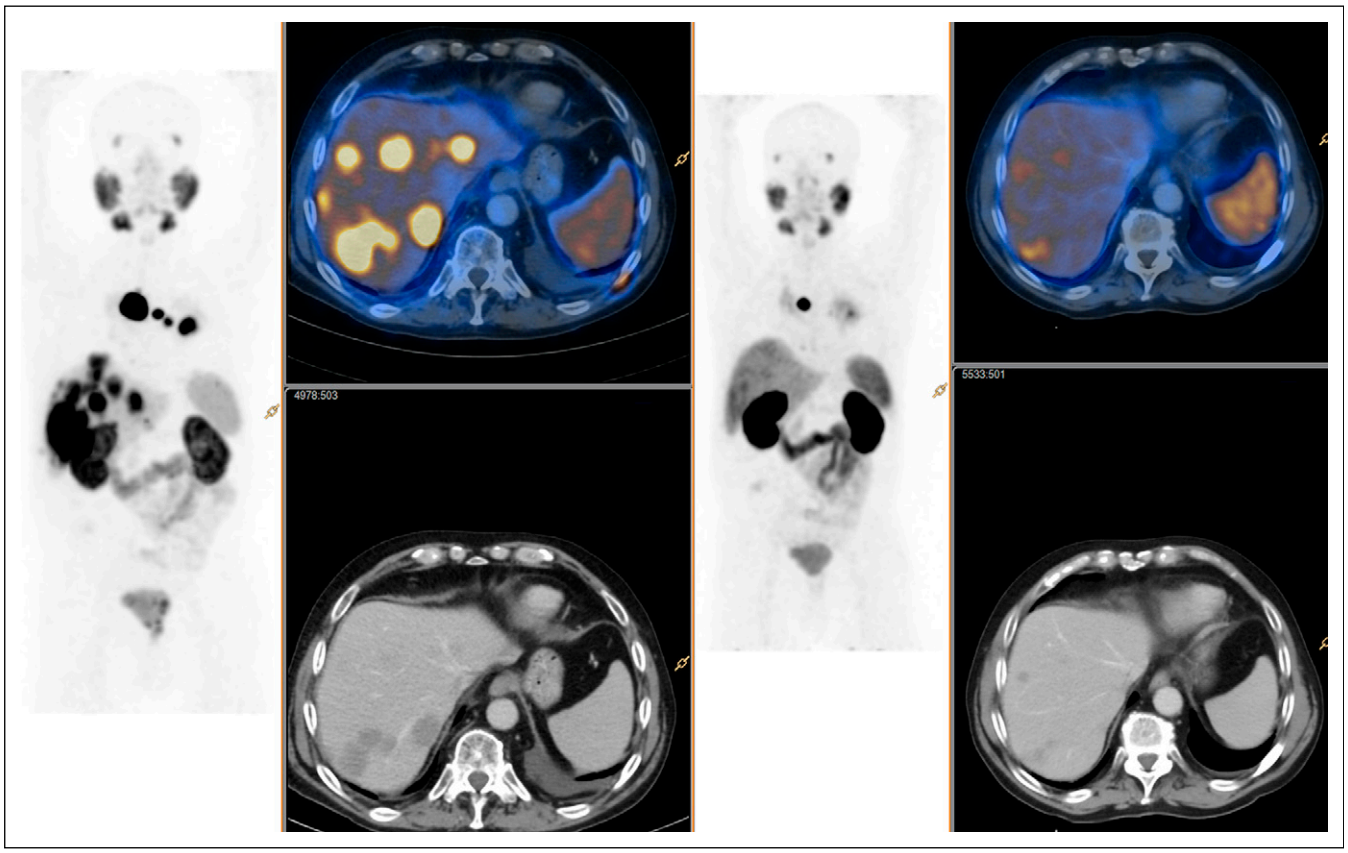

FIG 2. Selected images from pre- and post-treatment prostate-specific membrane antigen positron emission tomography scans with corresponding prostate-specific antigen levels showing metabolic and radiologic response to the hepatic metastases.

recombination genes, including a *BRCA2* frameshift deletion and missense substitutions in *ATM* (p.L2307F:CTT>TTT) and *BRIP* (p.R264W:CGG>TGG); the latter two were noted to likely be benign variants. To assess his germline, we performed targeted sequencing of coding regions and splice sites of *ATM, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, HOXB13, PALB2, PTEN, RAD51C, RAD51D, STK11,* and *TP53* on DNA extracted from blood; this confirmed a frameshift mutation in exon 11 of the *BRCA2* gene. Targeted next-generation sequencing was also performed on DNA extracted from his frozen archived primary prostatic tumor, screening 386 cancer-related genes. This tissue testing revealed biallelic *BRCA2* inactivation with the previously identified germline mutation (ENST00000380152[BRCA2]:c.5946delT [p.Ser1982ArgfsTer22]) as well as somatic loss of his wild-type allele. Analysis of his primary tumor also confirmed the presence of the benign variants identified in the ctDNA analysis as well as a variant in *CDH1* (L15del) that is not reported in the Catalogue of Somatic Mutations In Cancer or ClinVar.

DISCUSSION

PSMA, also known as glutamate carboxypeptidase II, is a transmembrane glycoprotein commonly overexpressed on prostate cancer cells.[5] The utility of PSMA as an imaging target has been demonstrated,[6] but its use as a therapeutic target is also evolving rapidly,[7] with a randomized phase II trial underway in Australia and a randomized phase III trial recruiting in the United States. Up-front resistance and early relapses are common, however, signifying the need for strategies to improve patient selection and/or test rational combination approaches.

As a form of ionizing radiation, ^{177}LuPSMA-617 induces double-strand DNA breaks, which are believed to be the main lethal event in most exposed cells. Cells rely on DNA repair mechanisms, such as homologous recombination and nonhomologous end-joining, to survive radiation-induced DNA damage. Preclinical and clinical studies have identified an association between cancers with homologous recombination defects and increased radiation sensitivity.[8] Germline mutations in genes that encode and mediate key enzymes for DNA repair pathways, such as *BRCA2* and *ATM*, occur in approximately 11.8% of men with metastatic prostate cancer and somatic mutations in at least 23% of patients with mCRPC,[3,4] rendering many prostate cancers homologous recombination deficient. Homologous recombination deficiency has been associated with responses to PARP inhibition and platinum-based chemotherapy,[9,10] but these treatments may cause significant toxicity.

This patient's germline mutation likely predisposed him to more aggressive disease,[11] and he was resistant to not only enzalutamide but also two lines of taxane-based chemotherapy. Interestingly, he did have a PSA response to external beam radiotherapy to his hilar disease. After his ^{177}LuPSMA-617 treatment, he also responded to carboplatin chemotherapy and a PARP inhibitor. It is biologically plausible that this gentleman's aberrations in homologous repair pathways enhanced his susceptibility to the radiation effects of ^{177}LuPSMA-617 therapy. We hypothesize that patients with mutations in DNA repair pathway genes would be especially responsive to peptide receptor radionuclide therapy because of their inability to overcome DNA breaks induced by the treatment. Prospective studies to test this hypothesis, clarify the relevance of specific variants, and explore the utility of ^{177}LuPSMA-617 in combination with other agents that target the DNA repair pathway are justified.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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