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Case Report

Exceptional Response to Everolimus in a Patient with Metastatic Castrate-Resistant Prostate Cancer Harboring a PTEN Inactivating Mutation

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PTEN · Prostate cancer · Everolimus · Castration resistant · mTOR

Abstract
Prostate cancer is among the most common types of cancer in men. Early detection and proper medical intervention is crucial to ensuring successful treatment. Here we describe a patient clinically presenting with castrate-resistant prostate carcinoma. Comprehensive genomic profiling identified a PTEN inactivating mutation in the patient's tumor. After being heavily pretreated, the patient showed stable disease on everolimus, a PI3K-Akt-mTOR pathway inhibitor.

Introduction

Prostate cancer (PC) is the most common non-cutaneous malignancy in men in the United States and accounts for over 26,000 deaths annually [1]. Androgen receptor (AR) signaling pathway inhibition has remained the cornerstone in the management of advanced PC for over 7 decades and identification of non-AR therapeutic targets in PC remains elusive. Prognosis for men who progress on AR-targeted therapy is dismal. Hence, there is an urgent and unmet need to identify non-AR targets which contain genomic alterations that would potentially respond to precision medicine strategies. Phosphatase and tensin homolog (*PTEN*) is a tumor

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Table 1. Variants detected in the patient's sample using comprehensive genomic profiling

Reportable alterations	
PTEN	N323fs*21
TP53	R273C
CDKN2A	loss
CDKN2B	loss
Variants of unknown significance	
BMPR1A	V450M
CARD11	N91S
ERBB3	splice site 404_421+60del78
FLT4	V1355M
NTRK1	R744H
PIK3C2G	V1313fs*8
ZNF703	H402_D403>PTHLGGSSCSTCSAHD
POLE	5' duplication

suppressor gene that has been targeted with success in patients with renal cell carcinoma and other malignancies; its inactivation leads to increased cell survival and proliferation because of hyperactivation of phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway [2, 3].

Here, we present the case of a patient with castrate-resistant prostate carcinoma (CRPC) who had failed multiple lines of treatment. He harbored a *PTEN* inactivating mutation and demonstrated an exceptional response to the mTOR inhibitor, everolimus (Afinitor; Novartis Pharma, Basel, Switzerland).

We also describe the genomic profiles from 261 consecutive cases of predominantly advanced PC harboring *PTEN* alterations and review the potential clinical utility of this class of alteration.

Case Report

A 67-year-old male was noted to have an elevated prostate-specific antigen (PSA) of 14 ng/mL during workup for nocturia. Further testing included a prostate biopsy that demonstrated Gleason grade 5 + 4 = 9 prostate adenocarcinoma in both lobes of the prostate and staging scans concerning for bone metastasis. He was started on a luteinizing hormone-releasing hormone agonist and bicalutamide. He had radiographic progression after only 7 months, and subsequent treatments included docetaxel, abiraterone, and cabazitaxel. Response to the above regimens was short-lived, with radiographic progression documented within 3 months on each line of treatment. Given treatment history including the rapid biochemical and radiographic progression, enzalutamide was not considered as the next appropriate line of treatment. Comprehensive genomic profiling (CGP) by a clinical next-generation sequencing hybrid capture-based assay using a formalin fixed, paraffin embedded prostatectomy specimen was performed by a CAP-accredited, CLIA-certified laboratory (Foundation Medicine, Cambridge, MA, USA) [4]. The test results showed that the tumor harbored an inactivating truncation mutation in *PTEN N323fs*21* (see Table 1 for all the alterations detected). Based on these results, everolimus was started at a dose of 10 mg oral daily. During treatment, his PSA remained stable, staging scans (including a bone scan and computerized tomography) showed no changes and he experienced no additional symptoms related to his disease. The dose was reduced to 5 mg oral daily after 3 months of treatment due to fatigue and cytopenias. Secondary to drug-related fatigue, after a total duration of 8 months of therapy, everolimus was discontinued (Fig. 1; Table 1; Table 2).

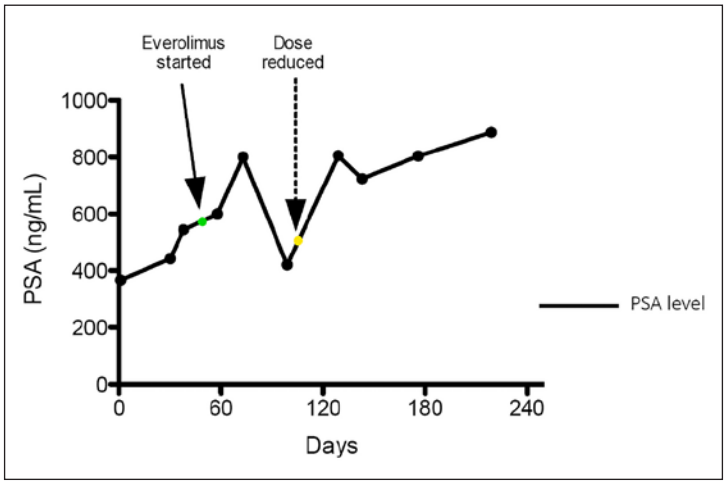

Fig. 1. PSA level over the course of treatment.

Table 2. PSA level of the patient over the course of treatment

Date	PSA, ng/mL		
26.11.2014	544		
06.12.2014		←	Started everolimus
16.12.2014	600		
31.12.2014	800		
26.01.2015	420		
25.02.2015	805	←	Scans showed stable disease, everolimus decreased to 5 mg due to fatigue
11.03.2015	724		
13.04.2015	804		
26.05.2015	887	←	Scans showed stable disease
01.07.2015		←	Discontinued everolimus due to clinical progression

Discussion

The present case underscores the potential clinical utility of genomic profiling in metastatic CRPC. The patient had received 3 of 6 approved therapies for CRPC, including docetaxel, cabazitaxel, and abiraterone. Sipuleucel-T, an autologous dendritic cell vaccine, was not considered appropriate as the drug is typically utilized in the pre-docetaxel space for asymptomatic or minimally symptomatic disease [5]. Radium-223, an alpha-emitting radio particle, could be considered for patients who are docetaxel refractory or ineligible [6]. This regimen was not chosen due to the rapidly rising PSA observed. Enzalutamide, a novel antiandrogen approved for use in the pre- and post-docetaxel setting based on the results from two phase III trials, was not considered due to emerging clinical data suggesting strong cross-resistance between enzalutamide and abiraterone [7–9].

All the above factors led to the decision to pursue CGP in the described patient, with the hope of identifying a pathway that could be potentially targeted with currently available drugs or with rational approaches in the context of a therapeutic clinical trial. It is estimated from the Cancer Genome Atlas (TCGA) analysis that homozygous deletions and inactivating mutations of *PTEN* occur in 40% and 5–10% of men with PC, respectively, but this data is based on a retrospective analysis of primary tumors, which may never progress to metastatic

disease [10]. We reviewed CGP results of 4,427 consecutive samples from patients with PS analyzed at Foundation Medicine during routine clinical care. Clinically relevant *PTEN* alterations inclusive of short variants, copy number losses, chromosomal rearrangements were detected in 1,423 patients (32.1%) with median age 66 years (range: 35–89). Homozygous deletion of *PTEN* was observed in 72.0% of these patients, with median age 67 (range: 39–89). Clinically relevant short variants and chromosomal rearrangements were detected in 25.0% of these patients, with median age 67 (range: 35–88) and 3.7% of patients with median age 65 (range: 47–86), respectively. 0.70% of patients had multiple *PTEN* alterations. Loss of heterozygosity in addition to a mutation in the other allele was recorded in 261 out of the 1,423 (18.3%) cases, including the index case. *PTEN* is thus bi-allelically inactivated in all 261 cases and the PI3K pathway is thus predicted to be activated. In contrast to the TCGA, the CGP described in this cohort is predominantly from heavily pretreated CRPC.

Functionally, *PTEN* is a tumor suppressor that negatively regulates the (PI3K)-AKT signaling axis. The PI3K and AR signaling pathways regulate each other through complex reciprocal feedback mechanisms. Upregulation of the mTOR pathway has been noted to confer resistance in CRPC cell lines and in CaP cells treated with ADT [11]. Similar crosstalk has been demonstrated between the estrogen receptor signaling pathway and the PI3K/AKT/mTOR pathway in breast cancer. Loss of *PTEN* expression was associated with inferior survival and shorter time on abiraterone treatment [12]. Loss of function hyperactivates mTORC1 signaling and is thought to confer sensitivity to rapamycin analogs such as everolimus.

Everolimus is FDA approved in the setting of advanced neuroendocrine cancers, hormone receptor-positive breast cancer, and renal cell carcinoma [13]. A phase II study examined everolimus in 37 patients with chemotherapy-naive mCRPC. A total of 13 patients (35.1%) had stable disease at 12 weeks. Two patients (5.4%) had PSA responses ≥50%. Notably, deletion of *PTEN*, although not specified as mono-allelic or bi-allelic, was associated with response to therapy, although this finding did not reach statistical significance [14]. A phase 2 clinical trial of everolimus and bicalutamide for CRPC demonstrated clinical activity; however, over 50% of patients had grade 3 or higher toxicity [15]. Similarly, several other studies also noted significant toxicity when PI3K/mTOR pathway inhibitors were combined with AR pathway inhibitors [16]. Several ongoing trials are combining novel antiandrogens (e.g., enzalutamide and ARN-509) with everolimus (NCT02106507; NCT02125084), although patients in most of these studies are not stratified by *PTEN* status. While the phase II experience provides evidence supporting everolimus in the context of CRPC prior to chemotherapy treatment, the case presented here suggests that everolimus can be effective in heavily pretreated disease in the context of a *PTEN* altered tumor. The prolonged period of radiographic disease stabilization (relative to three previously failed lines of treatment) suggests the possible broader efficacy of everolimus and the need to consider a sensitive and detailed assessment of the genomic status of *PTEN* for integration into the care of mCRPC patients. CGP can be used identify individuals with *PTEN* inactivating truncations, deletions, and homozygous losses to identify candidates for targeted therapy with everolimus and other PI3K-Akt-mTOR pathway inhibitors in development.

Conclusion

Everolimus is currently being investigated in chemotherapy-naive PC patients; however, our observation suggests clinical activity even in heavily treated mCRPC. Identification of *PTEN* inactivating truncations in mCRPC patients has potential clinical utility and warrants further investigation.

Statement of Ethics

Informed consent was obtained from the patient. The subject has given his written informed consent to publish his case. The authors have no ethical conflicts to disclose.

Disclosure Statement

J.A.K., N.A., Y.H., A.M.H., V.A.M., and J.S.R. are employees of and have equity interest in Foundation Medicine, Inc. V.A.M. is on the Board of Directors of Revolution Medicines and has received equity stake and compensation. S.K.P. has a research collaboration with Foundation Medicine Inc. S.M.A. is a former employee of Foundation Medicine, Inc., current SAB of Incysus Therapeutics, and does consulting for Revolution Medicines.

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Author Contributions

All the authors equally contributed to the preparation of the manuscript.

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