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Case Report

A Case Study Of A Patient With Metastatic Castration-Resistant Prostate Cancer With A Rad51b Alteration And Their Clinical Reaction To Rucaparib.

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Abstract

In patients with metastatic castration-resistant prostate cancer (mCRPC) linked to BRCA alterations, PARP inhibitors like rucaparib have been thoroughly studied. The clinical efficacy of these drugs has also been assessed in patients with mCRPC linked to changes in other nonBRCA DNA damage repair (DDR) genes, such as RAD51B. Depending on the particular DDR gene that has been changed, there is probably a varying sensitivity to PARP inhibition; however, because these gene modifications are not common, there is little research in this area. Here, we report a mCRPC patient with a truncating rearrangement of RAD51B who responded to treatment with the PARP inhibitor rucaparib in the TRITON2 trial in terms of both radiography and PSA.We used next-generation sequencing (NGS) of tissue and plasma to examine the patients' response characteristics, circulating tumor DNA (ctDNA) fraction, and tumor genomes over an extended period of time. The ctDNA proportion decreases during response and is correlated with both radiographic and PSA response. No possible genetic mechanism of acquired drug resistance was identified by NGS. In this instance, a rare patient with mCRPC and a RAD51B truncation exhibits signs of rucaparib activity.

Keywords : *prostate cancer; PARP inhibitors; RAD51B.*

INTRODUCTION

Numerous proteins, including the poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) enzymes, which are essential for repairing single-strand DNA breaks, and the homologous recombination repair (HRR)-related proteins BRCA1, BRCA2, and RAD51, facilitate DNA repair [1–3]. Through an interaction known as synthetic lethality, the enzymatic inhibition of PARP proteins causes DNA damage to accumulate and cell death in tumor cells with defective HRR (for example, due to gene change) [4-6].In the United States, patients with metastatic castration-resistant prostate cancer (mCRPC) associated with deleterious BRCA1 or BRCA2 (BRCA) mutations who have received androgen receptor-directed therapy and taxane-based chemotherapy can be treated with rucaparib, a PARP inhibitor [7].The efficacy findings of TRITON2 (NCT02952534), an international, multicenter phase II study of rucaparib in patients with mCRPC and homologous recombination repair deficiency (HRD), served as the basis for the rapid approval of rucaparib as a treatment for mCRPC patients [8].TRITON2 examined rucaparib treatment in a smaller group of patients with mCRPC who also had a non-BRCA DNA damage repair (DDR) gene modification [9], such as RAD51B, one of the RAD51 paralogs involved in the HRR pathway [3,10], in addition to assessing patients with a BRCA alteration. It is predicted that approximately 0.56% of patients with prostate cancer have harmful RAD51B mutations [11]. Since there is a dearth of information on patients with RAD51B mutations who received PARP inhibitor treatment, our case study of a patient with mCRPC and a RAD51B rearrangement is particularly noteworthy.

CASE REPORT

A 63-year-old man with no family history of cancer and a history of smoking was diagnosed with cT2 N0 M0 prostate cancer in April 2006. The pathology report identified the tumor as pT3a Nx adenocarcinoma with a Gleason score of 7 (3 + 4), and the patient underwent a radical prostatectomy. As an androgen deprivation therapy (ADT) for bone and lymph node metastases, the patient began long-term triptorelin in May 2014 and was prescribed a short-course bicalutamide (Figure 1A). After the diagnosis of mCRPC was established in February 2016, abiraterone was added to ADT. The patient responded

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best to this regimen in terms of stable disease; nonetheless, a rise in prostate-specific antigen led to the treatment's termination in October 2017 (87 weeks into the course). Pseud in October 2017 (87 weeks following treatment) as a result of elevated PSA levels (doubling time of 2 months) and verified bone and lymph node progression. After starting docetaxel in November 2017, the patient saw a PSA decrease of more than 50% and a confirmed partial response according to Response Evaluation Criteria In Solid Tumors, version 1.1 (RECIST). After stopping treatment in May 2018 (23 weeks, 8 cycles), PSA values started to increase within 8 weeks, and in late July 2018, the patient experienced enough pain to necessitate palliative radiation (1 × 8 Gy) for a spinal cord compression. In August 2018, the advancement of bone and nodal diseases was verified (Figure 2A).Based on the findings of genomic testing using the Foundation One next-generation sequencing (NGS) assay (Foundation Medicine, Cambridge, MA, USA) [12], which identified a truncating RAD51B rearrangement in an archival tumor tissue biopsy taken at the time of diagnosis (June 2006; Table 1), the patient was enrolled in the TRITON2 study in September 2018. Exons three through eleven of RAD51B's eleven exons were deleted as a result of the rearrangement, which involved a fusion with ACTN1. Furthermore, a harmful RB1 rearrangement and a pathogenic TMPRSS2-ERG fusion were found. NGS of a plasma sample obtained utilizing the Foundation before receiving rucaparib therapy Additional somatic pathogenic changes were found using one liquid CDx assay [13].Two TP53 mutations are among them (Table 1, Table S1). Using the Color Hereditary Cancer Test, all changes found were verified to be of somatic origin, and no further possible causes of the illness were found [14]. Rucaparib was administered to the patient for 107 weeks at the approved dose of 600 mg twice daily; however, hematologic toxicity, specifically anemia, caused multiple treatment interruptions and subsequent dose reductions to 200 mg twice daily (Figure 1A). The patient had several soft-tissue lesions in the left shoulder, left scapula, and more than ten bone-associated lesions at the beginning of TRITON2.and lymph nodes in the left axilla and latero-aortical region. For 80 weeks (December 2018 to July 2020), rucaparib treatment produced a confirmed partial response according to modified RECIST and/or Prostate Cancer Clinical Trials Working Group 3 criteria (maximum of 81% decrease in target lesion diameters; Figures 1B and 2A), with no evidence of bone progression. Additionally, the patient had a confirmed PSA response (≥50% decrease from baseline, validated by a second measurement ≥3 weeks later) (Figure 1B) that lasted for 64 weeks (October 2018 to January 2020) and had a maximal decline from baseline of 99%. By contrast, the median time to PSA progression was 15 of 27 TRITON2 patients with a BRCA mutation and a radiographic response, and the duration of response was ≥6 months.was 28 weeks for every patient with a TRITON2 BRCA mutation [8]. In September 2020, the patient stopped using the medication because of the clinical advancement of the disease at new locations in the left subclavicular and para-aortic areas (Figure 2B). After rucaparib medication was stopped, the patient was given 160 mg of enzalutamide daily from September 2020 to December 2020. The patient passed away in February of that year. Through genomic testing using the GuardantOMNI assay (Guardant Health, Redwood City, CA, USA) [15] of plasma samples taken at the beginning of treatment (September 2018 [week 1]), at the nadir of response (October 2019 [week 60]), and after a rise in PSA following the confirmed response (March 2020 [week 80]), the patient's longitudinal genomic profile was evaluated. and tracking development (September 2020 [week 108]) to learn more about the genetic environment. Less than 2% of cell-free tumor DNA was present in the on-treatment plasma samples taken around the time of best response, and the low (<10%) tumor fraction prevented the detection of the RAD51B rearrangement. The RAD51B truncation was discovered in the archival tumor sample taken at the time of initial diagnosis, in the plasma obtained prior to rucaparib treatment, and in the plasma obtained after progression. All plasma samples had a low tumor proportion, which varied from 1.3% while the radiographic response was at its greatest to 10.3% when treatment was initiated (Table 1). No secondary RAD51B mutations or other apparent causes of reversion were seen in the progression sample.

DISCUSSION

The clinical efficacy of rucaparib and other PARP inhibitors has been assessed in patients with mCRPC linked to changes in other non-BRCA DDR genes, such as RAD51B, although these medicines have arguably been better described in mCRPC related with BRCA mutations [16]. While men with mCRPC who had alterations in BRCA or ATM had a significantly longer median progression-free survival with olaparib compared to control agents (7.4 vs. 3.6 months; hazard ratio, 0.34 [95% CI, 0.25–0.47]; n = 245), the subgroup of patients with alterations in other DDR genes showed less pronounced effects (4.8 vs. 3.3 months; hazard ratio, 0.88; n = 142) in the phase III PROfound study (NCT02987543).Only seven of the genomically selected PROfound patients had an alteration in RAD51B, including one in the olaparib group with a co-occurring alteration in ATM and another in the control group with a co-occurring alteration in BRCA2. This suggests that there may be a differential sensitivity to PARP inhibition depending on the specific DDR gene altered, but research in this area is hampered by the low frequency of these alterations. The median imaging-based progression-free survival for patients with a truncated RAD51B rearrangement without a co-occurring DDR gene change (n = 5) was 1.8

months for the control group (n = 1) and 10.9 months for the olaparib group (n = 4) [16].We speculate that the tumor response to rucaparib in the TRITON2 patient presented here was most likely driven by HRD brought on by the truncating rearrangement of RAD51B. The plasma samples taken before and after rucaparib treatment, as well as the archival tumor sample taken at the time of initial diagnosis, had the RAD51B truncation. However, the on-treatment plasma samples at the time of response had very little circulating tumor DNA, and the RAD51B rearrangement was not visible. All plasma samples exhibited decreased sensitivity for deletion calling and a low tumor proportion. Therefore, it is impossible to completely rule out the possibility of another unidentified disease cause, like homozygous BRCA loss.Radiographic and PSA responses were produced by rucaparib treatment, and after a dose reduction to minimize side effects, rucaparib 200 mg twice day was continued to maintain the radiological response for more than a year. Eventually, the patient's left subclavicular and para-aortic regions developed additional lesions. The target lesions of the left axillary lymph nodes that existed before the beginning of rucaparib treatment, however, did not exhibit enlargement, indicating that the new lesions might have resulted from the formation of new cancer clones. Although no reversion mechanism or new genomic clones were found by NGS analysis of postprogression plasma, without NGS information from these novel lesions, This notion cannot be verified or disproved.In conclusion, this case demonstrates rucaparib activity in the only patient with a RAD51B genomic alteration enrolled in TRITON2, providing additional evidence that patients with mCRPC and DDR gene alterations other than BRCA1 or BRCA2 may also benefit clinically from PARP inhibitor treatment.

Author Contributions

Conception and design: B.S., A.L., S.P.W., W.A. Data collection (e.g., patient management and treatment): B.S., A.L., H.S. Data interpretation and analysis: All authors. All authors wrote, reviewed, and/or revised the manuscript. The published version of the manuscript has been read and approved by each author.

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Institutional Review Board Statement

TRITON2 was carried out in compliance with the International Council for Harmonization's Good Clinical Practice guidelines and the Declaration of Helsinki after being approved by national or local institutional review boards, including the University Hospital of Liège Ethics Committee on October 10, 2017, under protocol number 2017/85.

Informed Consent Statement

Prior to participation, the patient gave written informed consent, which included permission to publish data and/or pictures.

Data Availability Statement

Qualified researchers will be able to request de-identified datasets for the findings presented in this paper after sending a methodologically sound proposal to medinfo@clovisoncology.com. In accordance with applicable privacy laws, data protection, and permission and anonymization requirements, data will be made available for such requests for a period of one year after this article is published online. The information will come from Clovis Oncology. Neither a data dictionary nor identified participant data are shared by Clovis Oncology.

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Conflicts of Interest

Disclosures made by the authors about possible conflicts of interest: Sautois Brieuc, Advisory or Consultative Role: BMS Belgium, Astellas, Janssen, and Clovis Oncology Honoraria: Janssen: Andrea Loehr, MSD, Employment: Simon P. Watkins, Clovis Oncology, Stock and Other Ownership Interests: Clovis Oncology, Clovis Oncology, Wassim Abida, Clovis Oncology, Stock and Other Ownership Interests Honoraria: Roche, OncLive/MJH Life Sciences, Aptitude Health, Clinical Education Alliance, and Medscape Clovis Oncology, AstraZeneca/MedImmune, Daiichi Sankyo, Janssen, and ORIC Pharmaceuticals all have consulting or advisory roles. The following organizations are funding the research: Zenith Epigenetics (Inst), ORIC Pharmaceuticals (Inst), AstraZeneca (Inst), Clovis Oncology (Inst), and Epizyme (Inst). There were no other identified possible conflicts of interest.

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