Complete pathological remission after treatment with olaparib in a patient with PTEN-deficient sarcomatoid prostate cancer

Jue Wang

Abstract

Precision oncology utilizes the individual tumor genomic information to guide the optimal cancer treatment. In this case report, we describe a 67-year-old white male with T3N0M1, Gleason score 9 (5+4), prostate adenocarcinoma, who developed progressive urinary obstruction after seven months of treatment of luteinizing hormone-releasing hormone analog. A Computed Tomography (CT) scan detected large masses within the pelvis, involving the bladder and rectum. He underwent resection of tumor with pathology finding of carcinosarcoma transformation (sarcomatoid prostate cancer). Comprehensive genomic profiling identified multiple genomic alterations including TMPRSS2-ERG rearrangement, PTEN deletion, RB loss, and TP53 alteration. Based on the novel findings from next generation sequencing, he was treated with the oral Poly (Adenosine diphosphate) ADP-Ribose Polymerase (PARP) 1 inhibitor olaparib. CT scan after three months of therapy showed interval necrotic tumor changes of the heterogeneous prostate mass. The patient underwent pelvic exenteration to manage rectovescical fistula. Pathology showed complete pathological remission without residual tumor. This case highlights the potential of clinical next-generation sequencing in guiding the treatment decision of rare cancer when standard options fail, and thereby improving patient outcomes.

Key Words: Sarcomatoid prostate cancer; poly (ADP) ribose polymerase (PARP) 1 inhibitor; Olaparib, PTEN; TMPRSS2-ERG rearrangement; TP53, Complete pathological remission.

Materials and Methods

Pathological diagnosis and review of tumor samples were performed by members of pathology, St. Joseph’s Hospital and Medical Center, Phoenix, Arizona. Immunohistochemistry studies that pertinent to sarcomatoid carcinoma were used. Genomic profiling was performed in a (Clinical Laboratory Improvement Amendments) CLIA-certified, (College of American Pathologists) CAP-accredited reference laboratory (Foundation Medicine). DNA extracted from formalin-fixed paraffin-embedded tumor samples was analyzed by hybridization capture of 3,769 exons from 315 cancer-related genes and 47 introns of 19 genes commonly rearranged in cancer. At least 50 ng of DNA per sample was isolated and sequenced to high, uniform coverage (average 73X) on the Illumina HiSeq2500 instrument. Genomic Alterations (GA) (base substitutions, small insertions/deletions, rearrangements, and copy number alterations) were determined and reported. Actionable genomic alterations were defined as those with targeted anticancer drugs currently on the market or in registered clinical trials. Tumor Mutational Burden (TMB) was calculated from a minimum of 1.11 Mb of sequenced DNA and reported as mutations/Mb.

Case description

67 year old white male who initially presented to our cancer center with symptoms of urinary obstruction. His PSA was 2 ng/mL. Digital examinations showed enlargement of prostate. He subsequently underwent Transrectal Ultrasound (TRUS) guided prostate biopsy, showing adenocarcinoma of the prostate, Gleason score 9 (5+4). A Computed Tomography (CT) scan showed evidence of extracapsular extension, lymph node involvement, and TC-99 MDP (Technetium-99 Medronic acid) bone scintigraphy showed bone metastatic lesions. After treatment with a luteinizing hormone-releasing hormone analog for seven months, his PSA (Prostate Specific Antigen) became undetectable. Unfortunately, he developed recurrence of urinary obstruction seven months later, with radiographically detected masses within the pelvis and bladder with rectum involvement. On 12/10/2015, he underwent
transurethral resection of the prostate tumor which showed sarcomatoid prostatic adenocarcinoma (carcinosarcoma) involving the prostatic urethra and bladder neck and large mass extended into bladder. The malignant cells do not exhibit significant staining with antibodies directed against CK7, CK20 or desmin. The tumor exhibits focal reactivity with antibodies directed against cytokeratin AE1/AE3 as well as smooth muscle actin. The staining pattern is consistent with prostatic carcinosarcoma (sarcomatoid prostate cancer). Subsequently the patient progressed through multiple lines of therapies including chemotherapies (docetaxel) and chemoradiation.

Comprehensive Genomic Profiling (CGP) by Next-Generation Sequencing

The tumor tissue was further evaluated with next generation gene sequencing to evaluate for specific mutations. With Hybridization capture of 3,769 exons from 315 cancer-related genes and introns of 28 genes commonly rearranged in cancer; ≥ 50 ng of DNA, sequenced to high (average 756X), uniform coverage. Genomic alterations were identified including PTEN, RB deletion, TMPRSS2-ERG translocation, and TP53 mutation.

Treatment and outcome

His case was discussed at UACC (University of Arizona Cancer Center) molecular tumor board. Based on the findings of PTEN loss and TMPRSS2-ERG translocation which suggested that he may have increased sensitivity to a Poly (ADP)-ribose Polymerase (PARP) 1 inhibitor. Given the presence of potentially actionable alterations, and the patient’s progressive of disease through multiple lines of therapies, he provided consent and was started olaparib 400 mg PO twice a day therapy on August 3, 2016. The treatment was well tolerated with only occasional mild diarrhea, and fatigue. A repeated CT scan of abdomen and pelvis after one month of treatment showed heterogeneous pelvic mass arising from the superior prostate the measuring 8.7x6.1x8.8 cm, which was decreased from previous measurement of 10.1x9.6x12.9 cm. A repeated CT after three months of therapy showed interval necrotic tumor changes of prostate mass (Figure 1).

On December 27, 2016, the patient underwent pelvic exenteration to manage rectovesical fistula secondary to previous radiation therapy. Surgical pathology showed treatment effects, without residual disease (Table 1; Figure 2). His PSA at the time of cystoprostatectomy was <0.05 ng/mL.

DISCUSSION

Sarcomatoid carcinoma of the prostate is a rare and aggressive subtype of prostate cancer representing <1% of all prostate cancers [1-3]. Currently there is no standardized treatment regimen for SCP. We describe a patient with sarcomatoid prostate cancer with PTEN deletion, TMPRSS2-ERG translocation, RB loss, and TP53 mutation who was treated with olaparib after multiple lines of therapy and who had an impressive radiographic response and clinical benefit after 3 months of treatment. To our knowledge, this is the first reported case of sarcomatoid prostate cancer successfully treated with a PARP 1 inhibitor. Oncologists have been long observed considerable heterogeneity in clinical behavior and prognosis of prostate cancer. The results from our recent next generation gene sequencing profiling study [5] and genomic work up in this patient has provided fresh molecular insights into histogenesis of sarcomatoid prostate cancer. TMPRSS2-ERG is the most frequent genomic alteration described in localized prostate cancer, with 40–50% of patients harboring this translocation, and others harboring rearrangements involving other ETS family members [11]. Loss of PTEN and loss of TP53 are common genetic aberrations occurring in prostate cancer.

Table 1

<table>
<thead>
<tr>
<th>Date</th>
<th>Procedure</th>
<th>Pathology</th>
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<tbody>
<tr>
<td>5/16/2014</td>
<td>Prostate biopsy</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>9/24/2015</td>
<td>Transurethral resection of prostate</td>
<td>Adenocarcinoma, Gleason score 5+4</td>
</tr>
<tr>
<td>12/8/2015</td>
<td>Transurethral resection of prostate</td>
<td>Sarcomatoid prostate cancer (Carcinosarcoma)</td>
</tr>
<tr>
<td>12/27/2016</td>
<td>Cystoprostatectomy</td>
<td>No evidence of viable neoplasm</td>
</tr>
</tbody>
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Figure 1) (a) Computed tomography (CT) showing the heterogenous mass arising from the prostate bed. (b) Three months post therapy showing tumor necrotic changes.

Figure 2) (a) Tumor resection sample from bladder. Pathology consistent with prostatic carcinosarcoma (Sarcomatoid prostate cancer). (b) Pelvic exenteration sample showing treatment effects without residual disease.
A preclinical study demonstrated that PTEN and TP53 contribute to the regulation of self-renewal and differentiation in prostate progenitors, presumptive tumor initiating cells for prostate cancer [16-19]. In a Phase 1 dose-escalation clinical trial [20], Sandhu et al. treated 21 treatment refractory metastatic prostate cancer patients with PARP inhibitor niraparib. The investigators reported stabilization of disease in 43% of patients with a median duration of response of 254 days. In total, 30% of patients had a decrease of Circulating Tumor Cells (CTCs) and one of the 21 patients had >50% PSA reduction. Although the investigators did not observe correlation between ERG rearrangements/loss of PTEN expression and antitumor activity, however, they did not report any information specifically on the patients with TP53 alteration, RB loss, PTEN deletion, and TMPRSS2-ERG translocation. Next-generation molecular profiling may have a role in such rare neoplasms, by searching for actionable mutations that could guide treatment decision when standard treatment fail upon recurrence and disease progression. Patients such as this case show that the usefulness of molecular guided therapy in management of rare tumor such as sarcomatoid prostate carcinoma. Exploration of the molecular characteristics of tumors with exceptional responses is also an important tool in improving the use of the available targeted therapies we have at hand.

**CONCLUSION**

We describe here a case of sarcomatoid prostate carcinoma with complete response after three months of olaparib therapy in a patient with PTEN loss, RB deletion, TMPRSS2-ERG translocation, and TP53 mutation. Together with preclinical studies, our case provides clinical evidence of a potential role for PARP inhibitor treatment for PTEN-deficient tumors. Further prospective studies are needed to confirm the usefulness of novel biomarkers for PARP inhibitor sensitivity.

**REFERENCES**