Case Report

Acute Myeloid Leukemia After Olaparib Treatment in Metastatic Castration-Resistant Prostate Cancer

Jason Zhu,[1] Matthew Tucker,[2] Endi Wang,[3] Joel S. Grossman,[4] Andrew J. Armstrong,[1] Daniel J. George,[1] Tian Zhang[1]

Clinical Practice Points

- Prostate cancer is the third most common cause of cancer-related deaths among men in the United States. Twenty-five percent to 30% of sporadic castration-resistant prostate cancers are characterized by defects in DNA repair.
- Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors exploit defects in DNA repair to induce tumor-selective cytotoxicity and are in clinical development for treatment of prostate cancer.
- Serious adverse events might occur after the use of a PARP inhibitor for patients with metastatic castration-resistant prostate cancer. Long-term safety monitoring will be a necessary end point in evaluating the clinical benefit of PARP inhibitors in patients with genetically susceptible tumors.

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Introduction

Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors exploit defects in DNA repair to induce tumor-selective cytotoxicity and are in clinical development for treatment of prostate cancer. However, these agents may have lethal toxicities. This report highlights a serious adverse event after the use of a PARP inhibitor for a patient with metastatic castration resistant prostate cancer. Our patient had a complete response on olaparib treatment for prostate cancer, but developed likely treatment-related acute myeloid leukemia. Long term safety monitoring will be necessary in discussing clinical risks and benefits of PARP inhibitors for patients with genetically susceptible tumors.

Case

A 69-year-old man with metastatic prostate cancer was seen in clinic for evaluation and treatment in June 2013. At the time of diagnosis, his prostate-specific antigen (PSA) level was 12.85 ng/mL, and he had metastatic disease to the left acetabulum, left pelvic sidewall, and periurethral tissues. Transrectal ultrasound-guided biopsies of the prostate revealed Gleason 4 + 5 = 9 adenocarcinoma. Androgen deprivation therapy (ADT) was initiated with leuprolide. Seven months after ADT with leuprolide (January 2014), the patient had radiographic and PSA evidence of disease progression with new lesions in the pelvis, and he started abiraterone acetate and prednisone treatment. In addition, he received palliative radiation to the prostate (7650 centigray [cGy]), left acetabulum (6300 cGy), and pelvic lymph nodes. After radiation, his PSA declined to undetectable levels, and he was treated with sipuleucel-T (May 2014).

His cancer remained stable for 1 year, but he ultimately developed worsening metastatic disease in the penile shaft, iliac bones, and vertebral bodies (April 2015) and subsequently started chemotherapy with carboplatin (area under the curve 6) and docetaxel (75 mg/m^2). He had a good radiographic and clinical response and received a total of 3 cycles of chemotherapy. Genomic profiling of the primary tumor was also sent at this time, notable for mutation in partner and localizer of breast cancer susceptibility gene 2 (BRCA2) (*PALB2*), as well as *androgen receptor* amplification, *phosphatase and tensin homolog* loss, and *TMPRSS2-ERG* fusion. After the results of his genomic testing, his treatment was switched to olaparib (June 2015), and subsequent positron emission

[1]Division of Medical Oncology, Department of Medicine, Duke Cancer Institute
[2]Department of Medicine
[3]Department of Pathology, Duke University Medical Center, Durham, NC
[4]Florida Cancer Specialists and Research Institute, Naples, FL

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Address for correspondence: Tian Zhang, MD, Division of Medical Oncology, Department of Medicine, Duke Cancer Institute, DUMC 103861, Durham, NC 27710
E-mail contact: tian.zhang2@dm.duke.edu

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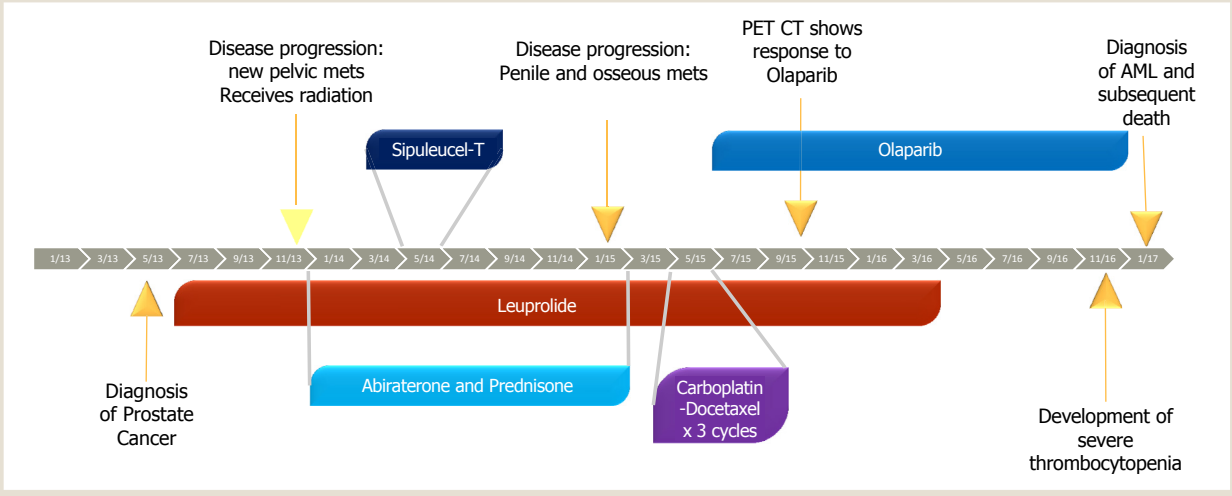
Figure 1 Patient Timeline



Abbreviations: AML = acute myeloid leukemia; CT = computed tomography; mets = metastases; PET = positron emission tomography.

tomography (PET) scans over the following 16 months (September 2015, April 2016, and October 2016) showed decreased to stable metastatic disease (Figure 1). His soft tissue disease on his penile shaft completely resolved and his only evaluable disease was noted on 18F-sodium fluoride PET/computed tomography imaging, suggesting a complete response. Overall, he tolerated olaparib well except for some decreased appetite, taste changes, and increase in indigestion and nausea. He also had Grade I pancytopenia and nausea but did not require any supportive red blood cell transfusions until September 2016. He had such a dramatic response with olaparib that leuprolide was discontinued and even with a recovering testosterone level, his PSA remained undetectable.

Eighteen months after the initiation of olaparib (December 2016), he presented to his local emergency room with fever and fatigue, and was found to have pancytopenia. Laboratory values were notable for a white blood cell count of 2.7×10^9/L (absolute neutrophil count 1.3×10^9/L), hemoglobin 8.8 g/dL, and platelets 35×10^9/L. He underwent a bone marrow examination; the bone marrow aspirate smear showed a marked erythroid hyperplasia with increased pronormoblasts and prominent dysplasia (Figure 2A), and marked decrease in myelopoiesis and megakaryopoiesis. Of note, there was active histiocytic phagocytosis of hematopoietic elements, with many dysplastic erythroid precursors internalized (Figure 2B). The bone marrow biopsy section showed marked hypercellularity (90%; Figure 2C) with hyperplasia of blastic cells (Figure 2D). These blastic cells were positive for E-cadherin (Figure 2E) and glycophorin A (Figure 2F), the 2 lineage-specific antigens for erythroid precursors. The concurrent flow cytometric analysis detected 62% phenotypically abnormal erythroid precursors that expressed CD71, CD235a and aberrant CD56 (dim). The morphologic features and immunophenotypic findings of his bone marrow examination supported the diagnosis of pure erythroid leukemia (acute myeloid leukemia [AML] M6b according to French-American-British classification). Chromosomal analysis showed clonal abnormalities with complex changes in all 20 metaphase cells. Unfortunately, shortly after diagnosis, his hospital course was complicated by hypoxic respiratory failure secondary to pneumonia, and he died 1 week after the diagnosis of AML.

Discussion

Treatment of Prostate Cancer With Poly(adenosine diphosphate-Ribose) Polymerase Inhibitors

Metastatic castration-resistant prostate cancer (mCRPC) is known to have multiple candidate driver mutations in genes associated with DNA repair, androgen receptor signaling, histone/chromatin modification, along with classic tumor suppressors and oncogenes.[1] PARP are a family of multifunctional enzymes that play a critical role in cell differentiation, transformation, as well as the repair of DNA single-strand breaks.[2] Poly(ADP-ribose) polymerase (PARP) inhibition can lead to the accumulation of DNA double-strand breaks at replication forks, which are typically repaired by key components of the DNA repair complex scaffolded by BRCA1 and BRCA2.[3] For tumors that carry a loss of function *BRCA1/2* mutation or other mutations affecting the DNA repair complex, PARP inhibitors might exploit this defect to induce tumor-selective cytotoxicity, sparing normal cells.[4] Several PARP inhibitors are currently in clinical development for treatment of multiple solid tumors and AML (Table 1).[5-8] Olaparib (Lynparza; AstraZeneca, Wilmington, DE) is an oral, first in class PARP inhibitor that is currently approved by the US Food and Drug Administration for the treatment of patients with germline BRCA-mutated advanced ovarian cancer.[5] Furthermore, olaparib has been investigated in patients with mCRPC; TOPARP-A (phase II trial of olaparib in patients with advanced metastatic resistant prostate cancer) was an open-label single arm multisite study in which 50 patients were treated with olaparib at a dose of 400 mg twice a day.[9] Patients were stratified into 2 groups, biomarker positive and biomarker negative. Patients were considered biomarker positive if a homozygous deletion or deleterious mutation was identified in a gene reported to be involved in the DNA damage repair pathway or

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