Case Report

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

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## 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

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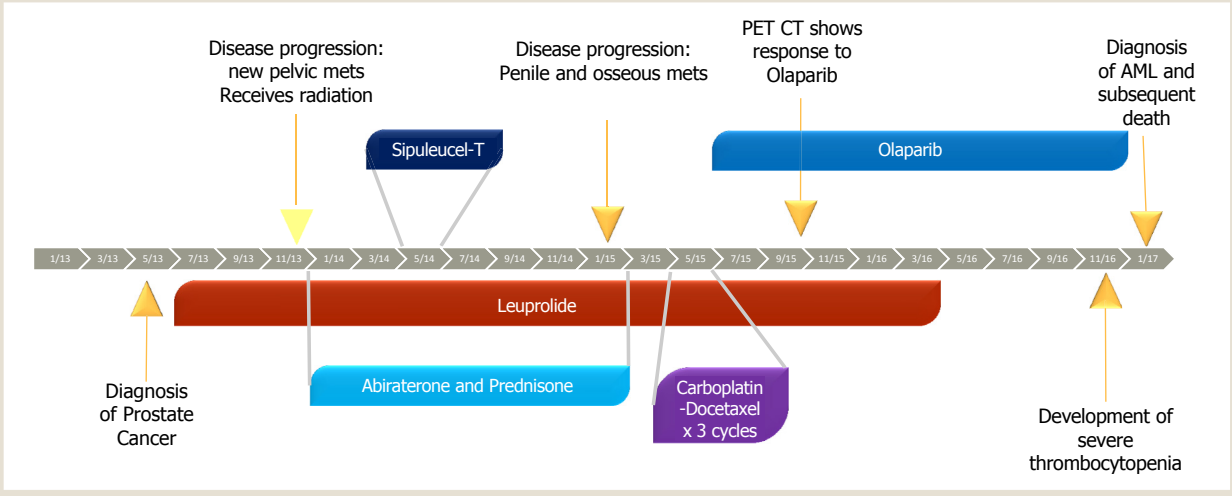
**Figure 1** Patient Timeline




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.

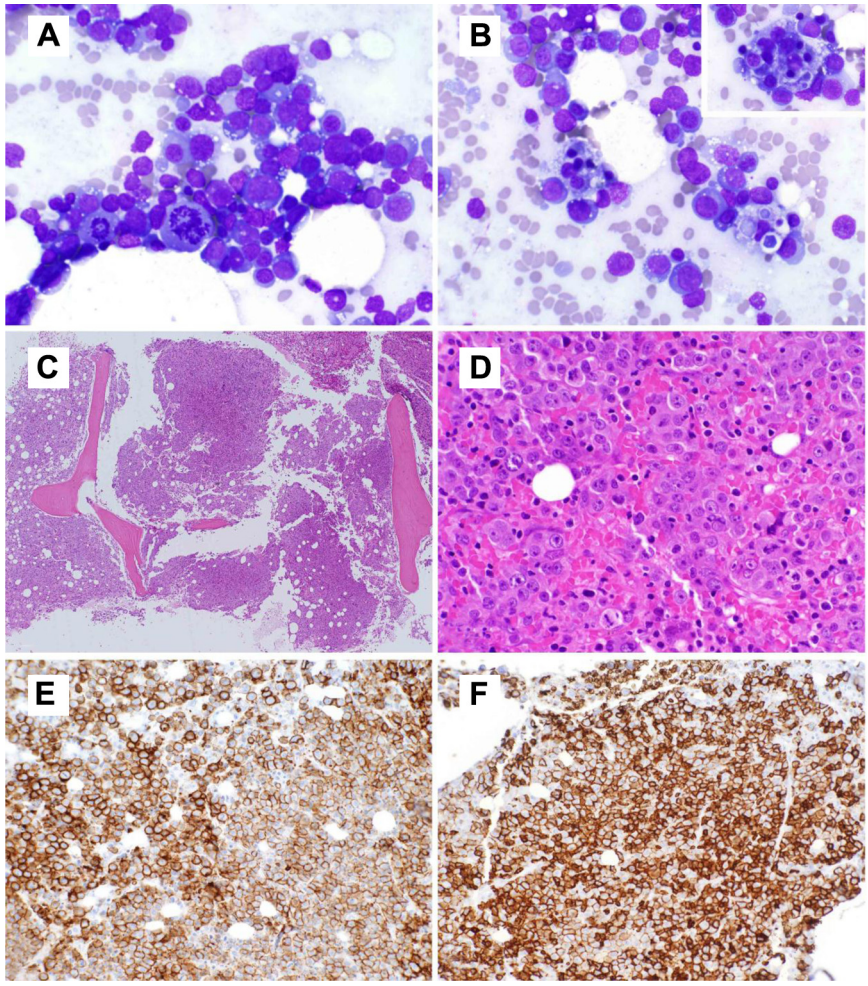
Eighteen months after the initiation of olaparib (December 2016), he presented to his local emergency room with fever and fatigue, and was found to have pancytopenia. Laboratory values were notable for a white blood cell count of $2.7 \times 10^9$/L (absolute neutrophil count $1.3 \times 10^9$/L), hemoglobin 8.8 g/dL, and platelets $35 \times 10^9$/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

**Figure 2** **Bone Marrow Examination. (A) Bone Marrow Aspirate Smear Showing Marked Increase in Erythroid Precursors and Decrease in Other Hematopoietic Elements. Note the Increased Fraction of Early Erythroid Precursors Such as Pronormoblasts, and Dysplastic Changes Including Cytoplasmic Vacuoles and Karyorrhexis. Wright-Giemsa Stain, Magnification ×400. (B) Bone Marrow Aspirate Smear Showing Active Histiocytic Hematophagocytosis. Wright-Giemsa Stain, Magnification ×400. (C) The Core Section Showing Bone Marrow Hypercellularity. Hematoxylin and Eosin (H & E) Stain, Magnification ×40. (D) A High Magnification Shows Bone Marrow Replacement by Large Blastic Cells. H & E Stain, Magnification ×400. (E) Immunohistochemical Stain for E-Cadherin Shows Delicate Membranous Staining in Large Blastic Cells. Magnification ×200. (F) Immunohistochemical Stain for Glycophorin A Exhibits Membranous Staining in Many Cells Including Those With Blastic Morphology**




sensitive to PARP inhibition. Sixteen patients were found to be biomarker positive, and 14 (88%) of those patients had a response to olaparib, with a median radiographic progression-free survival of 9.8 months versus 2.7 months in the biomarker-negative group ($P < .001$). The most common adverse events were anemia (76%), fatigue (58%), and nausea (36%).

### *Partner and Localizer of BRCA2*

Partner and localizer of BRCA2 (PALB2) is an important component of the homologous recombination repair, involved in linking BRCA1 and BRCA2 to form a BRCA complex that is essential in preventing cells from accumulating DNA damage.[10,11] Another name for PALB2 is Fanconi anemia complementation group N (FANCN), a key component of the Fanconi anemia DNA repair pathway. Patients with Fanconi anemia who carry *PALB2* and *BRCA2* mutations have an 800-fold increased risk of myelodysplastic syndrome (MDS) or AML when both alleles are inherited.[12] Our patient in this case report had a mutation in *PALB2* (d616fs*12). Germline *PALB2* mutations are rare—in a retrospective review of 692 men with metastatic prostate cancer, 3 men (0.4%) had a germline *PALB2* mutation.[13] Somatic mutations are equally rare, only identified in 0% to 2% of patients with localized and metastatic prostate cancer.[14] Although these DNA repair defects were the same ones that allowed the patient to have a good response to olaparib, they are the same mutations that might have contributed to the development of therapy-related AML.

**Table 1** Poly(ADP-Ribose) Polymerase Inhibitors in Clinical Development

| Name | FDA-Approved Indications | Clinical Trial Setting | PARP Trapping Activity |
|---|---|---|---|
| **Olaparib** | Monotherapy in patients with deleterious or suspected deleterious germline BRCA-mutated (detected using an FDA-approved test) advanced ovarian cancer who have been treated with ≥3 previous lines of chemotherapy[5] | Prostate cancer, recurrent ovarian, primary peritoneal, or fallopian tube cancer, GBM, small-cell lung cancer, endometrial cancer, gastric cancer, NSCLC | (+++)[6] |
| **Rucaparib** | Treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with ≥2 chemotherapies[7] | Prostate cancer, ovarian, fallopian tube, or primary peritoneal cancer patients | Not directly compared |
| **Niraparib** | Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in complete or partial response to platinum-based chemotherapy[8] | Ewing sarcoma, ovarian cancer, breast cancer, prostate, endometrial | (++++)[6] |
| **Veliparib** | Not FDA-approved. In clinical trials | Pancreatic cancer, refractory testicular germ cell cancer, small cell lung cancer, breast cancer, metastatic epithelial ovarian, primary peritoneal cavity, or fallopian tube cancer | (+)[6] |
| **Talazoparib** | Not FDA-approved. In clinical trials | Ovarian cancer, or primary peritoneal cancer, AML, breast | Not directly compared |

Abbreviations: ADP = adenosine diphosphate; AML = acute myeloid leukemia; BRCA = breast cancer susceptibility gene; FDA = US Food and Drug Administration; GBM = glioblastoma multiforme; NSCLC = non–small-cell lung cancer; PARP = poly(ADP-ribose) polymerase; +++ = degree of PARP trapping reported in literature.

### *Treatment-Related AML*

Although there were no reported cases of therapy-related leukemia in the TOPARP-A study, treatment-related MDS/AML is rare but has been reported as a complication of olaparib treatment.[15] In a separate phase II study olaparib was evaluated in patients with germline BRCA1/2 mutations and metastatic ovarian, breast, pancreatic, and prostate cancers.[11] Two of the 9 deaths in this phase II study were due to treatment-related leukemia,[16] and a third patient in the study developed MDS. All 3 patients had been heavily pretreated with previous chemotherapy (from 25 to 34 cycles) before olaparib exposure. Olaparib might further increase the risk in pretreated patients with germline DNA repair deficiencies by enhancing the impairment of a critical repair pathway by means of PARP inhibition. For example, olaparib causes "PARP trapping," binding PARP when it is already bound to DNA and causing double strand breaks, therefore inducing more DNA damage than other PARP inhibitors that inhibit PARP when free-floating in the nucleus or cytoplasm.[6]

Therapy-related AML is a well described complication of chemotherapy.[17] Interestingly, in the TOPARP-A study, 100% of the participants had received chemotherapy before PARP inhibition, and there were no reported cases of treatment-related AML with a median follow-up of 14.4 months.[9] Our patient had exposure to chemotherapy—3 cycles of carboplatin and paclitaxel—and therefore had higher risk for developing AML from exposures to chemotherapy as well as PARP inhibitor.

Although AML after olaparib treatment has never been described in literature for prostate cancer, there are numerous studies that described the rates of MDS and AML after radiotherapy. The results have been inconsistent—some studies of patients who received radiotherapy versus surgery for localized prostate cancer have reported no difference in the risk of developing leukemia, whereas others report an increased rate of AML among those who received external beam radiation compared with those who did not.[18,19] Wang et al performed a large retrospective cohort study of 32,000 elderly prostate cancer patients who had not been exposed to chemotherapy, and reported that patients who had been treated with intensity-modulated radiotherapy had an increased risk of secondary MDS/AML.[20] Since the addition of radium-223 to the arsenal of treatments for mCRPC, there have also been 2 case reports of AML developing after exposure to radium-223 therapy.[21,22] In addition to previous chemotherapy, our patient also had pelvic radiation (6300 cGy) which could have further increased his risk for developing treatment-related AML.

In the natural history of prostate cancer, a patient might be exposed to many leukemogenic therapies, including radiation and chemotherapy. These therapies might have an additive effect and further increase risk of developing a treatment-related leukemia from PARP inhibitors, especially in our older patient population. It is important to note that this case occurred after 1 year of treatment and at a time when the patient was believed to be in complete remission. Future screening with bone marrow biopsies or treatment breaks should be considered in the future when using this class of therapy for heavily pretreated advanced prostate cancer patients.

## Conclusion

This report offers a cautionary warning for the development of PARP inhibitors in patients with mCRPC and DNA damage repair defects. ClinicalTrials.gov currently features more than 9 phase II/III studies using PARP inhibitors for the treatment of mCRPC, with 7 actively recruiting trials.[23] Long-term safety will be a necessary end point in evaluating the clinical benefit of these agents in these patients with genetically susceptible tumors.

## Disclosure

The authors have stated that they have no conflicts of interest.

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