Biallelic Inactivation of BRCA2 in Platinum-sensitive Metastatic Castration-resistant Prostate Cancer

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1. Case report

Treatment for metastatic castration-resistant prostate cancer (mCRPC) now includes taxanes, androgen receptor pathway inhibitors, active cellular therapy, and a bone-targeting radiopharmaceutical [1]. Predictive biomarkers are needed to guide treatment selection and sequence. Reports describing the mutational landscape of mCRPC hold great promise for precision medicine, but actionable treatment decisions remain unclear [2–4].

Platinum chemotherapy is infrequently used for prostate cancer (PCa) except in cases of neuroendocrine differentiation [5]. We identified three patients with non-neuroendocrine mCRPC with an exceptional response to platinum, defined as patients with advanced cancer who attain a complete or partial response lasting at least 6 mo when expected response is ≤20%. To identify molecular changes associated with exceptional response, we retrospectively performed clinical targeted next-generation sequencing on tumor DNA. Surprisingly, the common finding between all three was biallelic inactivation of BRCA2, the homologous recombination DNA repair gene.

Patient 1 was diagnosed at age 66 yr with prostate-specific antigen (PSA) of 24.8 ng/ml and Gleason 4 + 4 prostate
adenocarcinoma and underwent neoadjuvant androgen deprivation therapy (ADT) on a clinical study followed by radical prostatectomy and salvage radiotherapy. After 4 yr, he was found to have metastases to the liver, lymph nodes, and bone. Biopsy of liver metastases revealed adenocarcinoma without evidence of neuroendocrine differentiation.

He received docetaxel with a PSA decline from 136 to 59 ng/mL, followed by PSA rise and then treatment with abiraterone followed by enzalutamide, both resulting in PSA decline. Unfortunately, he developed worsening malignant pleural effusions and ascites and ultimately elected to transition to hospice.

DNA sequencing of the metastatic liver biopsy revealed two BRCA2 mutations, p.Q3066X and an exon 11 partial deletion on separate alleles (Table 1).

Patient 1 did not have a significant family history of cancer despite clear evidence of an inherited deleterious BRCA2 mutation on germline testing. In light of these findings, he was referred to the medical genetics department, and mutation was confirmed.

Patient 2 was diagnosed at age 53 yr with PSA of 6.8 ng/mL and Gleason 5 + 4 prostate adenocarcinoma and underwent radical prostatectomy followed by salvage radiotherapy with ADT. After 5 yr, his PSA had risen to 12.0 ng/mL, and bone metastases were identified. He received 3 yr of intermittent ADT. On developing castration resistance, he was treated with abiraterone and then enzalutamide; both resulted in transient control and then PSA rise (Fig. 1B) and progressive disease. He then received docetaxel with no response, followed by carboplatin/doxorubicin for 6 mo with PSA and clinical response. Sequencing of a metastatic biopsy identified two deleterious BRCA2 frameshift mutations including one that was germline (Table 1).

Patient 2 had a family history suggestive of a high-penetrance germline mutation with both father and paternal grandfather with PCa and a paternal aunt with breast cancer. He was referred to the medical genetics department, and mutation was confirmed.

Patient 3 was diagnosed at age 70 yr with PSA of 4.9 ng/mL and Gleason 5 + 5 prostate adenocarcinoma metastatic to pelvic and retroperitoneal lymph nodes. He developed castration resistance 6 mo after initiating ADT and was found to have liver metastases when PSA reached 10.0 ng/mL. Metastatic liver biopsy was obtained to assess for neuroendocrine differentiation, which was ruled out with immunohistochemistry. He was treated with docetaxel/carboplatin with a near-complete radiographic and PSA response (Fig. 1C). He was subsequently treated with abiraterone with disease progression and went on to receive a second course of docetaxel/carboplatin with another near-complete radiographic and PSA response. He then received “maintenance” carboplatin for >2 yr of progression-free survival. Sequencing of the previously obtained liver biopsy revealed somatic homozygous BRCA2 copy loss in the metastasis (Table 1, Fig. 2). We were unable to confirm the

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**Table 1 – BRCA2 mutations identified**

<table>
<thead>
<tr>
<th>BRCA2 mutations</th>
<th>Mutation type</th>
<th>Germline</th>
<th>Primary</th>
<th>Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Allele 1</td>
<td>c.9196C&gt;T; p.Q3066X</td>
<td>Premature stop</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Allele 2</td>
<td>127bp del in exon 11</td>
<td>Frameshift deletion</td>
<td>X</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Allele 1</td>
<td>c.8904delC; p.V2969fs*7</td>
<td>Frameshift deletion</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Allele 2</td>
<td>c.2611delT; p.S871Qfs*3</td>
<td>Frameshift deletion</td>
<td>X</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Allele 1</td>
<td>Homozygous copy loss</td>
<td>Copy loss</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Allele 2</td>
<td>Homozygous copy loss</td>
<td>Copy loss</td>
<td>X</td>
</tr>
</tbody>
</table>

1. Mutations are reported using reference transcript NM 000059.3.
2. Low tumor purity limited detection of somatic mutations.
The prevalence of inactivation of BRCA2 and other DNA damage repair genes in mCRPC is higher than previously thought and will require further validation. In one report, 7 of 50 (14%) patients with lethal PCa were found to have alterations in BRCA2 [2]. The whole-exome sequencing results of the initial 150 mCRPC metastases from the SU2C Prostate International Dream Team demonstrated that 19% had aberrations in DNA repair genes (a combination of somatic and germline) including BRCA1, BRCA2, and ATM [4].

Inheritance of deleterious BRCA2 mutations is well established to increase the risk of developing PCa in addition to breast, ovarian, pancreas, and other malignancies. Male BRCA2 mutation carriers with localized PCa are at substantially higher risk of dying from PCa than their non-mutation-carrying counterparts [7]. Together with the SU2C data, this suggests that biallelic inactivation (germline and somatic) of BRCA2 and related homologous recombination genes may be enriched among patients with aggressive mCRPC, especially when compared with the broader population of all (mostly indolent) PCa.

Our case series provides evidence that homozygous inactivation of BRCA2 in mCRPC may confer sensitivity to platinum agents. Our series is limited by its small numbers and retrospective nature, but it suggests that inactivation of BRCA2 and other DNA repair genes could be clinically useful as predictive biomarkers of platinum response. Whether other patients with hemizygous or homozygous inactivation of BRCA2 or those with inactivation of other DNA repair pathway genes will be sensitive to DNA-damaging agents can only be addressed in prospective studies.

To our knowledge, this report is the first to associate dramatic response to platinum in men who had mCRPC and who were unselected for a priori mutation carriage with biallelic loss of BRCA2. Our report adds substantively to prior case reports that known BRCA2 mutation carriers with mCRPC may respond particularly well to platinum chemotherapies. This mirrors breast and ovarian cancers, in which platinum chemotherapies are commonly used, and evidence suggests that germline and somatic mutations in homologous recombination genes such as BRCA2 are associated with response to platinum and overall survival [8].

BRCA1/2 mutation carriers have also been effectively treated with a poly (ADP-ribose) polymerase inhibitor (PARPi) that renders synthetic lethality in cells with defective homologous DNA repair. Dramatic responses to PARPi have been reported very recently by Mateo et al [9]. Among men with mCRPC no longer responding to standard therapies whose tumors had evidence of DNA repair defects (including BRCA2, ATM, Fanconi anemia genes, and CHEK2), treatment with the PARPi olaparib resulted in a response rate of 88% (14 of 16) [9]. Clinical studies testing platinum agents, in combination and/or in sequence with PARPi, should also be explored for the subset of mCRPC patients whose tumors have biallelic inactivation of BRCA2 and related homologous recombination repair pathway genes.

In the context of emerging data that BRCA1/2 mutations may be present in up to 20% of mCRPC [4] and that BRCA2 mutation–associated PCa is more aggressive [7], we are heartened by the dramatic platinum responses in these three patients whose tumors carried biallelic inactivation of BRCA2. Collectively, recent findings present a strong case for larger studies evaluating the tumors of all men who develop metastatic PCa for biallelic inactivation of BRCA2 and related homologous DNA repair genes. These appear to be likely predictive biomarkers for treatment response to DNA-damaging therapy such as PARP inhibition and the widely available platinum chemotherapies.

3. Methods

We identified 14 patients with mCRPC treated with docetaxel and carboplatin between 2010 and the present. Although there was no standard institutional approach to treating patients with docetaxel and carboplatin, none had evidence of neuroendocrine differentiation, and most had aggressive features such as visceral involvement. Overall, 5 of 14 patients (36%) achieved treatment response, defined as PSA decline by 50% or radiographic partial response. Three patients had tumors available for analysis and are reported here. All three patients provided written informed consent for review of their medical record and sequencing.
of their primary and metastatic PCa tissue. Research was conducted with University of Washington institutional review board approval.

DNA was extracted from formalin-fixed paraffin-embedded (FFPE) samples, as previously described [10]. Slides stained with hematoxylin and eosin were reviewed before DNA extraction for all FFPE samples, and when feasible, macrodissection of tumor areas was performed to enrich tumor cellularity. We performed sequencing with UW-OncoPlex (University of Washington, Seattle, WA, USA), a validated clinical molecular diagnostic assay that collects simultaneous deep-sequencing information, based on >500 times average coverage, for all classes of mutations in 194 targeted clinically relevant genes, as previously reported [10]. At the time of this writing, 31 patients with PCa have undergone tumor sequencing with UW-OncoPlex at our institution. Four of 31 (13%) were identified to have biallelic BRCA2 inactivation, 1 of whom died before results became available and without receiving platinum chemotherapy. The cases of the three others were reported in this paper.

Conflicts of interest: The authors have nothing to disclose.

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References

EU-ACME question

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Question:

In addition to the potential association of biallelic inactivation of BRCA2 with sensitivity of metastatic castration-resistant prostate cancer to platinum chemotherapy reported in this case series, there is evidence in the literature to support the following statements:

A. When an inactivating BRCA2 mutation is identified in germline DNA, there may be an increased risk of prostate cancer in addition to breast, ovarian, and pancreatic cancers.
B. There is a higher risk of prostate cancer–associated death among prostate cancer patients who are BRCA2 mutation carriers compared with noncarriers.
C. Recent data suggest that up to 20% of metastatic castration-resistant prostate cancers may contain biallelic inactivation of DNA damage repair genes such as BRCA2.
D. All of the above.

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