Case Report

Prominent response to platinum-based chemotherapy in a patient with BRCA2 mutant-neuroendocrine prostate cancer and MDM2 amplification

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Abbreviations & Acronyms
AR = androgen receptor
BRCA2 = breast cancer susceptibility gene
CN = copy number
CRPC = castration-resistant prostate cancer
HRR = homologous recombination DNA repair
LOH = loss of heterozygosity
MDM2 = Murine Double Minute 2
NEPC = neuroendocrine prostate cancer
PSA = prostate-specific antigen
RB1 = retinoblastoma 1
SPOP = speckle-type bric-a-brac, tramtrack, broad complex/pox virus and zinc finger protein
VAF = variant allele frequency

Introduction: Genomic profiling provides useful information for diagnosis, treatment, and prognosis, and detection of certain defects, such as DNA repair gene aberrations or microsatellite instability, can possibly lead to optimal treatment, but this testing has not been widely used to inform prostate cancer treatment.

Case presentation: A 55-year-old man sequentially treated for prostate cancer was diagnosed as neuroendocrine prostate cancer from prostate specimens resected because of urinary retention. Subsequently, he received five cycles of platinum-based chemotherapy in total and responded well. We also performed next-generation sequencing of a sample from the prostate specimen and identified a BRCA2 mutation with MDM2 amplification and loss of heterozygosity in RB1.

Conclusion: We report a neuroendocrine prostate cancer patient with Murine Double Minute 2 amplification who experienced an aggressive course and for whom platinum-based chemotherapy was effective, and one of the reasons for the good response might be the BRCA2 mutation.

Key words: MDM2, BRCA2, neuroendocrine prostate cancer, genomic profiling.

Keynote message
Next-generation sequencing identified a BRCA2 mutation, MDM2 amplification, and LOH in the RB1 gene, although there was no tumor protein p53 mutation. This patient with NEPC was treated with platinum-based chemotherapy and experienced good response to the chemotherapy, and one of the reasons for the good response might be the BRCA2 mutation. One of genetic features of NEPC is inactivation of p53 and, in this case, p53 was inactivated due to MDM2 amplification.

Introduction
Genomic profiling is useful for diagnosis, treatment, and prognosis of various diseases and conditions, such as DNA repair gene aberrations or microsatellite instability, and the information can possibly lead to optimal treatment for cancer patients. However, it has not been widely used to inform prostate cancer treatment. We report a case of an NEPC patient with MDM2 amplification and LOH in RB1 who exhibited an aggressive course and responded well to platinum-based chemotherapy.

Case presentation
The patient was a 55-year-old man who presented to a nearby hospital with a symptom of frequent urination. He had no family medical history. His serum PSA level was 426.9 ng/mL. Pathological analysis revealed prostate adenocarcinoma with a Gleason score of 4 + 5.
Magnetic resonance imaging revealed that the prostate cancer had grown outside of the prostate. Computed tomography and bone scans showed pelvic lymph node swelling and multiple bone metastases at the lumbar vertebra and ilium. Imaging examination revealed stage cT3aN1M1b prostate cancer. Subsequently, the patient underwent androgen deprivation therapy and denosumab. He was sequentially treated with therapeutic agents (Fig. 1a). During cabazitaxel treatment, his PSA level gradually increased, and imaging examination revealed new metastases in the pubic bone and right external iliac lymph nodes (Fig. 1b). Moreover, he then developed urinary retention due to local progression of prostate cancer. Subsequently, he was referred to our hospital for further treatment. First, he received transurethral resection of the prostate to relieve his urinary retention. The pathological diagnosis of the prostate specimens was adenocarcinoma with neuroendocrine differentiation (Fig. 2a). Immunohistochemical analysis showed positivity for synaptophysin, chromogranin A, and androgen receptor, although PSA was only partially positive. However, serum neuron-specific enolase level was within normal limits before the operation.

Therefore, the patient received chemotherapy using carboplatin (area under the curve = 5) with etoposide (100 mg/m² intravenous infusion on days 1–3). He received five cycles of platinum-based chemotherapy in total. The patient was free from a urethral catheter, and the prostate volume and lymph node sizes were reduced remarkably on radiography after the chemotherapy (Fig. 1c), and his PSA level gradually went down (Fig. 1a).

In addition, we performed targeted next-generation sequencing of the resected prostate specimen by applying certain algorithms and the list of 160 genes examined (Appendix S1 and Table S1). A BRCA2 frameshift mutation (p.N2346Qfs*20) with LOH was detected as a pathogenic variant in the tumor. The VAF% in this case was 55.4%; however, this patient did not have a family history, such as of hereditary breast and ovarian cancer or prostate cancer. MDM2 amplification (estimated CN: 4.6) and myc proto-oncogene, basic helix-loop-helix transcription factor amplification (estimated CN: 4.0) were observed. LOH was observed in RB1 and Fanconi anemia complementation group A. The tumor mutation burdens calculated from our pipeline were 5.4 single-nucleotide variants/Mbp in the samples. The CN variation box and VAF plots (Fig. 2b,c) indicated a high LOH frequency and scattered allelic imbalance, which are often detected in homologous recombination-deficient tumors.

**Discussion**

Although a variety of new therapeutic agents, such as enzalutamide, abiraterone acetate, and cabazitaxel, are used to treat CRPC patients, only a few CRPC patients achieve remission, and most experience disease progression. Although platinum-based chemotherapy is sequentially not used for the treatment of CRPC, it has been reported to be effective for some CRPC patients. In a systematic review, Leal and García-Perdomo found that platinum-based chemotherapy was effective for patients with CRPC to some extent, and Aparicio et al. reported that patients with some variants of CRPC and an atypical and aggressive clinical course were characterized by sensitivity to platinum-based chemotherapy. We have also reported that CRPC patients with genetic alterations, such as SPOP and BRCA2 mutation, showed drastic responses to cisplatin-based chemotherapy. However, there is no
Fig. 2  (a) Representative images of immunohistochemistry of the transurethral resection of prostate specimens for synaptophysin, chromogranin A, AR and PSA. Bars indicate 100 μm. (b, c) The horizontal axis corresponds to the examined genes, and the vertical axis corresponds to (b) the CN or (c) variant allele frequency.
consensus on what kind of CRPC patients can benefit from platinum-based chemotherapy.

Recently, some studies have shown that DNA repair gene aberrations, such as mutations of *BRCA1/2* and *ataxia telangiectasia* mutated, are biomarkers for the higher likelihood response of platinum chemotherapy and poly(adenosine diphosphate-ribose) polymerase inhibitor. Those genetic mutations are present in 20% of metastatic CRPCs. In this case, a *BRCA2* mutation was identified, and VAF plots (Fig. 2b) indicated the potential of a high LOH frequency and scattered allelic imbalance. Recently, three independent DNA-based measures of genomic instability reflecting underlying tumor HRR deficiency have been developed on the basis of LOH, telomeric allelic imbalance, and large-scale state transitions. However, we could not determine the homologous recombination deficiency score because the relevant test did not undergo, and therefore, could not prove this. However, we can hypothesize that the *BRCA2* mutation results in an HRR deficiency subsequently causes a high LOH frequency and scattered allelic imbalance, which potentially results in a good response to platinum chemotherapy.

Furthermore, some reports have indicated that genetic features of NEPC are inactivation of the RB and p53, and some researchers have reported *MDM2* as one of the regulators of p53. Overexpression of *MDM2* inhibits p53 activity thorough p53 ubiquitination and inhibition of p53 interaction with DNA and leads to tumor progression. *MDM2* is upregulated in almost 30% of prostate cancer patients and associated with distant metastasis. However, the association between NEPC and *MDM2* has rarely been reported to date. In this NEPC case, next-generation sequencing identified a *BRCA2* mutation, *MDM2* amplification, and LOH in the *RB1* gene, although there was no *tumor protein p53* mutation. In this case, LOH was observed in the *RB1* gene. Thus, we believe that the other allele may be inactivated by *RB1* promoter methylation or epigenetic change, which induced the loss of *RB1* functionality. Genetic analysis suggested that *RB1* inactivation and p53 inactivation due to *MDM2* amplification after sequential treatment could have led to the NEPC of this patient.

Testing DNA alterations and checking those DNA repair gene aberrations might be beneficial to patients with aggressive CRPC from the point of view of precision oncology. In this case, a *BRCA2* mutation had already been detected by genetic testing; therefore, we planned to use a poly(adenosine diphosphate-ribose) polymerase inhibitor after platinum-based chemotherapy. Here, we report an NEPC patient with *MDM2* amplification who experienced an aggressive course and for whom platinum-based chemotherapy was effective because of a *BRCA2* mutation.

**Conflict of interest**

The authors declare no conflict of interest.

**References**

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**Supporting information**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Table S1**. 160 genes examined in the PleSSision-Rapid test.

**Appendix S1**. Materials and methods.

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**Editorial Comment**

**Editorial Comment to Prominent response to platinum-based chemotherapy in a patient with BRCA2 mutant-neuroendocrine prostate cancer and MDM2 amplification**

In this issue, Daimon *et al.* reported on the efficacy of platinum-based chemotherapy in patients with neuroendocrine prostate cancer harboring *BRCA2* mutations. Docetaxel administered after progression to castration-resistant prostate cancer (CRPC) initially suppressed disease progression, but prostate-specific antigen (PSA) levels remained constantly elevated during the subsequent administration of enzalutamide and cabazitaxel. Eventually, the patient was pathologically diagnosed as adenocarcinoma with neuroendocrine differentiation. After