



Case Report

Prostate cancer recurring as small-cell carcinoma with a *BRCA2* somatic mutation

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Abbreviations & Acronyms

PARP = poly ADP-ribose polymerase

BRCA2 = breast cancer susceptibility gene

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Introduction: Small-cell carcinoma of the prostate has a poor prognosis, and treatment options for the refractory disease are unclear.

Case presentation: A 68-year-old man with prostate cancer was referred to our hospital. He was treated with combined androgen blockade (bicalutamide and degarelix acetate). The disease progressed to castration-resistant prostate cancer, but with additional treatment, prostate-specific antigen levels remained below 0.02 ng/mL. However, computed tomography revealed enlarged right inguinal lymph nodes; moreover, his neuron-specific enolase levels were elevated. Histopathologic analysis of a biopsied lymph node confirmed small-cell carcinoma. After administering cytotoxic chemotherapy (etoposide plus cisplatin and amrubicin), the patient temporarily improved before relapsing. After genetic testing of the biopsy specimen revealed a *BRCA2* deletion, we administered the oral PARP-2 inhibitor olaparib, which has achieved partial remission for 8 months.

Conclusion: PARP-2 inhibition may improve the survival of patients with *BRCA2*-positive small-cell carcinoma of the prostate.

Key words: *BRCA2* gene, PARP inhibitor, prostate cancer, small-cell carcinoma.

Keynote message

Small-cell carcinoma of the prostate (SCCP) is considered a type of neuroendocrine tumor. There are no guidelines for treating refractory SCCP. However, we reported a patient with SCCP carrying a *BRCA2* mutation who benefitted from the PARP-2 inhibitor olaparib after repeated relapses, indicating that this route may be a subsequent-line therapy for patients with this tumor type.

Introduction

Small-cell carcinoma of the prostate (SCCP) is a malignant neoplasm exhibiting neuroendocrine differentiation, and is an aggressive disease with a poor prognosis.¹ It is treated as neuroendocrine prostate cancer (NEPC) that can be managed with cytotoxic chemotherapy; however, the overall survival rate is 8 months from initial NEPC diagnosis.² Olaparib, which is a PARP-2 inhibitor, has been shown to be effective against *BRCA1/2*-mutant prostate cancer (PC) and was introduced in Japan in 2020.³ We report a patient with SCCP carrying a *BRCA2* somatic mutation that was controlled by olaparib.

Case presentation

A 68-year-old man was referred to our department for the treatment of his PC. His initial serum prostate-specific antigen (PSA) level was 18.9 ng/mL (Fig. 1), and all his 14 prostate biopsy cores comprised almost totally of adenocarcinoma. His Gleason score was 4 + 5, and his clinical stage diagnosis was cT2cN0M0. Although we suggested androgen deprivation therapy combined with radiotherapy, he refused the latter owing to concerns about aggravating his preexisting ulcerative colitis. Therefore, he was treated only with combined androgen blockade comprising bicalutamide and degarelix acetate. Fourteen months after commencing

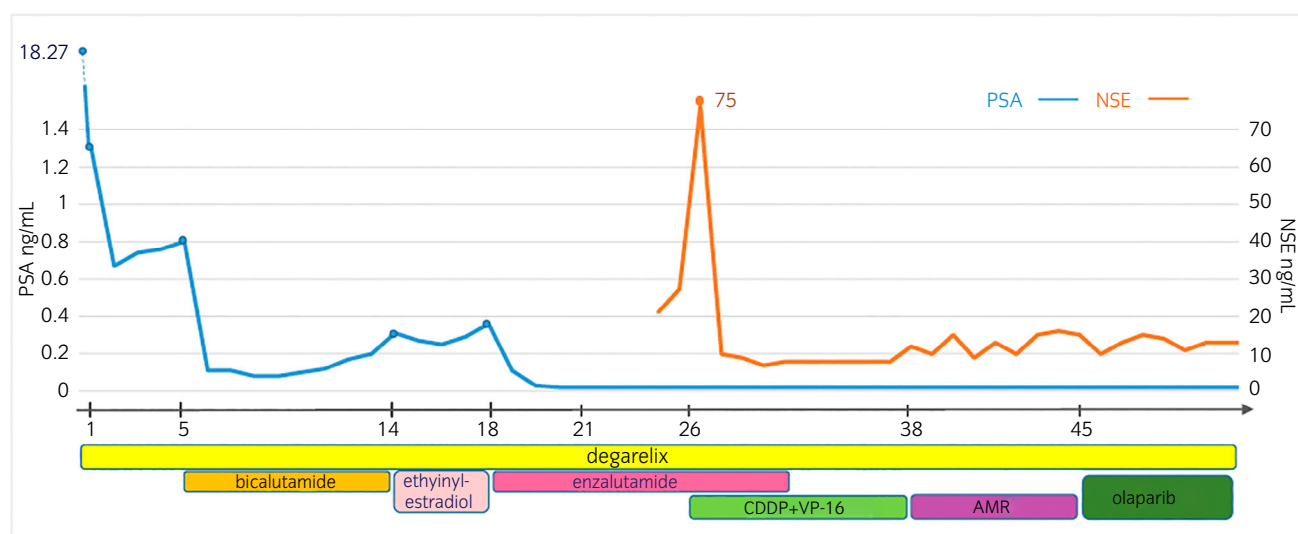


Fig. 1 PSA, prostate-specific antigen; NSE, neuron-specific enolase.

treatment, the disease progressed to non-metastatic castration-resistant PC (CRPC). At that time, his neuron-specific enolase (NSE) level was 15 ng/mL (normal range, <12 ng/mL). We switched his oral regimen from bicalutamide to ethinylestradiol and subsequently to enzalutamide. Ultimately, he consented to undergo intensity-modulated radiotherapy (76 Gy in 38 fractions) to the prostate in combination with enzalutamide and degarelix acetate.

Although his PSA level decreased and remained under 0.02 ng/mL, computed tomography (CT) 6 months later revealed abnormal right inguinal lymph nodes; moreover, his NSE increased to 21 ng/mL. We performed a biopsy of a metastatic lymph node in the right inguinal area; pathological examination revealed characteristics typical of SCCP, including positive immunohistochemical staining of synaptophysin, chromogranin A, and CD56 (Fig. 2). Since no other primary

small-cell carcinoma lesions were detected, he was deemed to have metastatic SCCP 15 months after the CRPC diagnosis. During this time, the disease rapidly progressed, and NSE increased to 75 ng/mL.

Next, we administered the combination chemotherapy of etoposide and cisplatin once every 3 weeks according to the regimen recommended for small-cell lung cancer (SCLC). At the end of the third course, his NSE decreased to 7 ng/mL, and CT showed metastatic lymph node shrinkage (Fig. 3a,b). Since his PSA remained continuously low, we ceased enzalutamide administration. At the time of administering the eleventh course, however, his NSE increased to 15 ng/mL. Magnetic resonance imaging showed infiltration of local prostate lesions to the bladder and the seminal vesicle (Fig. 3c).

Next, we administered amrubicin, but after transient improvement, its effectiveness waned; new lymphadenopathy

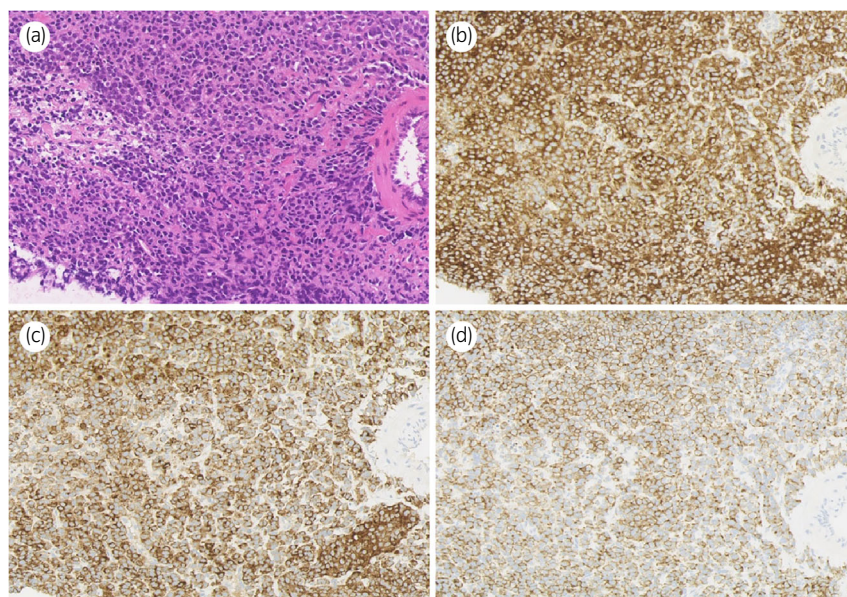


Fig. 2 Pathological analysis of the metastatic lymph node excised from the patient's right inguinal area. The lymph node biopsy showed a diffuse, solid growth pattern with a high nuclear-to-cytoplasmic ratio and fine nuclear chromatin pattern (a, hematoxylin and eosin staining; 20×). Immunohistochemical analysis showed positive staining for synaptophysin (b, 20×), chromogranin A (c, 20×), and CD56 (d, 20×).

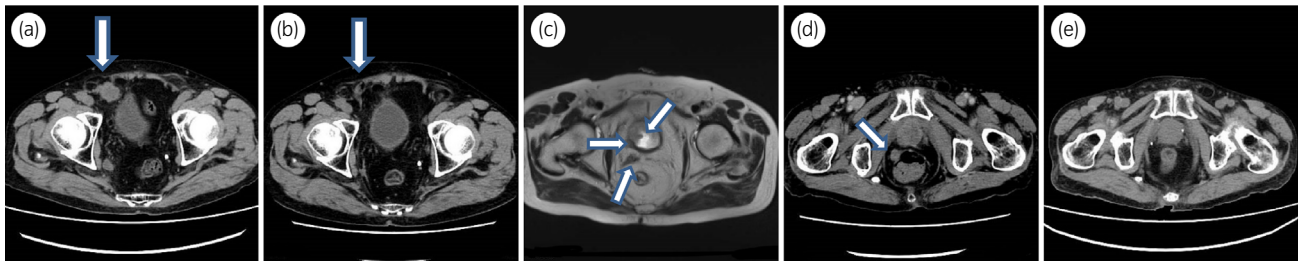


Fig. 3 Imaging of the patient's prostate cancer. Computed tomography (CT) revealed a metastatic lymph node in the right inguinal area, and a biopsy was performed on this lesion (a). At the end of the third course of etoposide and cisplatin therapy, CT showed shrinkage of the lymph node metastasis and disappearance of peritoneal dissemination (b). At the time of administering the eleventh course of etoposide and cisplatin therapy, magnetic resonance imaging revealed infiltration of local prostate lesions into the bladder and seminal vesicle (c). After administering 6 courses of amrubicin, novel lymph node swelling appeared (d). After olaparib treatment, the lymph node shrank (e).

and bone metastases appeared after 6 courses (Fig. 3d), his NSE rose to 15 ng/mL, and pain in his perineum and back worsened.

At this time, we were uncertain as to how to proceed. Therefore, we thought that olaparib could be used as a PARP inhibitor if there was a BRCA1/2 mutation, so we decided to carry out a genetic test. Genetic testing (FoundationOne CDx; Foundation Medicine, Cambridge, MA) of the previously biopsied lymph node specimen revealed *BRCA2* loss of heterozygosity with base substitution mutation (Table 1). Therefore, we administered olaparib, a PARP-2 inhibitor shown to be effective in patients with *BRCA2* mutations. His severe pain improved after commencing treatment, and the lymph node shrank (Fig. 3e). Olaparib treatment thereby achieved partial remission that has continued for 8 months after initiation; his NSE levels currently range between 12 and 15 ng/mL.

Discussion

SCCP is classified as a subtype of NEPC and accounts for less than 1% of all PCs.⁴ Androgen deprivation therapy (particularly using the new generation of agents such as abiraterone acetate and enzalutamide) is reportedly associated with an increased risk of NEPC.⁵ Since PSA and prostate-specific membrane antigen are not secreted by NEPC, NSE, and progastrin-releasing peptide are used as tumor markers

instead.^{6,7} Fluorodeoxyglucose-positron emission tomography-CT can be useful for detecting NEPC, as this tumor type tends to be metabolically active.⁸ It was reported that some NEPC lesions were successfully identified using ¹¹¹In-pentetreotide, which detects somatostatin receptor activity⁹; while this test was negative for our patient (data not shown), we quickly determined the diagnosis to be SCCP.

There are currently no clear treatment guidelines for NEPC. The National Comprehensive Cancer Network (NCCN) guidelines (version 4.2019) for PC point to the recommendations of the NCCN guidelines version 2.2018 for SCLC or alternative CRPC therapies based on clinical and pathological features.¹⁰ For our patient, we administered cisplatin/etoposide and amrubicin according to the NCCN guidelines for SCLC after discussions with the in-hospital ethics committee. However, there are no recommendations for subsequent refractory disease. Although previous studies of SCLC indicated that immune checkpoint inhibitors such as atezolizumab with platinum chemotherapy and nivolumab plus ipilimumab could be beneficial, investigations focused on NEPC have not yet been performed.^{11,12} In this case, these treatments before olaparib were effective for a relatively long time (19 months) until progression disease.

BRCA1/2 mutations are present in 0.44% and 1.2% of patients with PC,^{13,14} and in 0.87% and 5.35% of those with metastatic CRPC, respectively.¹⁵ One-half of *BRCA1/2* gene

Table 1 The classification of the detected gene mutation

Total				
14	Genetic mutations that are clearly associated with cancer			
	Total	Mutation (base sequence/insertion/deletion)	Changes in the number of copies	Chromosomal rearrangement
	2	1	1	0
		RB1[splice site c.137+1G>T]	BRCA2[loss]	---
12	Genetic mutations of unknown association with cancer			
	Total	Mutation (base sequence/insertion/deletion)	Changes in the number of copies	Chromosomal rearrangement
	12	11	0	1
		BRCA2[p.H415R]	CSF3R[p.N493Y]	---
		GATA6[p.H448Y]	CUL4A[p.S78C]	EWSR1 rearrangement intron 8
		NOTCH1[p.P1227S]	EZH2[p.D191H]	
		PDGFRA[p.D1033V]	IKBKE[p.G660E]	
		KEL[p.R14H]	NOTCH1[p.D1185N]	
		BRCA2[p.K1132R]		

mutations in CRPC are reportedly of germline origin, while the remainder (including in our patient) are somatic.¹⁶ *BRCA1/2* mutations are associated with an aggressive PC phenotype and are more likely to induce progressive disease leading to poorer survival.¹⁷ However, PARP inhibitors such as olaparib have recently been reported to be effective against *BRCA* mutation-carrying tumors,³ and NEPC may be no exception.

Reports regarding treatment options for patients with NEPC carrying *BRCA* mutations are sparse. Pandya et al. found that olaparib administered as a maintenance therapy to a patient with NEPC carrying germline *BRCA2* mutations led to survival for 18 months post-NEPC diagnosis.¹⁸ Herein, we report another patient with SCCP who benefitted considerably from olaparib.

In summary, NEPCs (including SCCP) have no established treatment strategy, but PARP inhibitors may be considered as one of the treatments for such diseases with *BRCA2* mutations.

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None.

Author contributions

Ryo Yabusaki: Writing – original draft. Koji Yoshimura: Writing – review and editing. Keisei Taku: Visualization. Makoto Suzuki: Visualization.

Conflicts of interest

The authors declare no conflicts of interest.

Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

Informed consent

The patient consented to the publication of this case report and corresponding images.

Registry and the Registration No. of the study/trial

Not applicable.

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