Case Report

Treatment-related neuroendocrine prostate cancer with *BRCA2* germline mutation treated with olaparib

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Abbreviations & Acronyms
ABI = abiraterone
ADT = androgen-deprivation therapy
AWD = alive with disease
BCL = bicalutamide
CAB = combined androgen blockade
CBDCA = carboplatin
CBZ = cabazitaxel
CD = cancer death
CDDP = cisplatin
CRPC = castration-resistant prostate cancer
DTX = docetaxel
ENZ = enzalutamide
ETP = etoposide
GOS = goserelin
HRD = homologous recombination deficiency
HRR = homologous recombination repair
LPR = leuprolide
N/A = not available
NED = no evidence of disease
NEPC = neuroendocrine prostate cancer
NSE = neuron-specific enolase
PSA = prostate-specific antigen
PARP = poly(ADP-ribose) polymerase
proGRP = pro-gastrin-releasing peptide
RP = radical prostatectomy
RT = radiation therapy
t-NEPC = treatment-related neuroendocrine prostate cancer

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How to cite this article: Ikeda R, Matsuoka Y, Inoue M *et al*. Treatment-related neuroendocrine prostate cancer with *BRCA2* germline mutation treated with olaparib. *IJU Case Rep*. 2024; 7: 115–119.

Received 10 September 2023; accepted 29 November 2023.
Online publication 8 December 2023

Introduction: The efficacy of olaparib for treatment-related neuroendocrine prostate cancer is unknown. Here, we report a case of treatment-related neuroendocrine prostate cancer with a *BRCA2* mutation that was treated with olaparib with 1-year efficacy.

Case presentation: A 75-year-old man initially diagnosed with prostate adenocarcinoma developed treatment-related neuroendocrine prostate cancer after 10-year androgen deprivation therapy. Despite the initial temporary effects of etoposide and carboplatin, the patient experienced prostate bed tumor recurrence 1 year after chemotherapy cessation. FoundationOne® detected a *BRCA2* gene mutation, and olaparib was initiated after repeating one chemotherapy course using the same chemotherapeutic agents. The patient received olaparib with sustained tumor regression for 1 year without severe side effects.

Conclusion: Olaparib may be the treatment of choice for treatment-related neuroendocrine prostate cancer in patients with *BRCA* mutations.

Key words: *BRCA2*, castration-resistant, neuroendocrine tumor, poly(ADP-ribose) polymerase inhibitors, prostate cancer.

Keynote message

A 75-year-old man initially diagnosed with prostate adenocarcinoma developed treatment-related neuroendocrine prostate cancer 10 years after androgen deprivation therapy was initiated. Chemotherapy with etoposide and carboplatin was effective; however, the patient experienced prostate bed tumor recurrence 1 year after chemotherapy. FoundationOne® detected *BRCA2* gene mutation, and olaparib has been used with sustained tumor regression for 1 year.

Introduction

PARP is critical in DNA damage repair. Olaparib, its selective inhibitor, exploits synthetic lethality against CRPC with HRD.[1] t-NEPC, a CRPC status after androgen deprivation therapy (ADT), is characterized by either low or absent androgen receptor expression, small-cell carcinoma morphology, and expression of neuroendocrine markers.[2]

In most cases with t-NEPC, the efficacy of chemotherapy is limited, and the prognosis is extremely poor.[3] Mutations in HRR genes, including breast cancer gene (*BRCA*) mutation, are rare in t-NEPC,[4] and the efficacy of olaparib for t-NEPC remains unclear. Here, we report a case of t-NEPC with a *BRCA2* mutation that was treated with sustained tumor regression for 1 year.

Case presentation

In 2008, a 64-year-old man with a serum PSA level of 6.5 ng/mL and a family history of breast and prostate cancers was diagnosed as having cT3N0M0 prostate cancer. Prostate biopsy revealed adenocarcinoma with a Gleason score of 4 + 5. The patient underwent a prostatectomy 3 months after receiving neoadjuvant hormonal therapy. One year after surgery, salvage ADT was introduced for biochemical recurrence, and the PSA level was <0.02 ng/mL. In

2015, the patient progressed to non-metastatic CRPC, with elevated PSA levels and local recurrence in the pelvic floor. The disease was controlled with salvage radiotherapy (74 Gy/37 Fr) to the pelvic floor, with decreased serum PSA levels. NSE and proGRP levels were 12.5 ng/mL (normal: <16.3 ng/mL) and 53.8 ng/mL (normal: <67 pg/mL), respectively, at the end of salvage radiotherapy.

In 2019, the PSA levels decreased to 0.001 ng/mL. However, NSE and proGRP levels increased to 31.8 ng/mL and 65.8 pg/mL, respectively, despite low PSA levels. Imaging revealed a resurgence of the pelvic floor tumor and mediastinal and pelvic lymph node metastases (Fig. 1a,b). Biopsy of the pelvic floor tumor revealed small malignant cells with a high nuclear-to-cytoplasmic ratio, and frequent mitotic figures were arranged in diffuse sheets (Fig. 1c,d). Immunohistochemical analysis showed that the tumor was positive for synaptophysin, CD56, and chromogranin A but negative for PSA (Fig. 1e–g). Based on the appearance of tumor cells and positive findings for neuroendocrine markers, the recurrent tumor was pathologically diagnosed as small-cell NEPC and clinically diagnosed as t-NEPC. Adenocarcinoma components were not detected.

The clinical course after NEPC diagnosis is shown in Figure 2. Four-month chemotherapy with ETP and CBDCA resulted in a complete response. However, in 2021, the pelvic floor tumor recurred again (Fig. 3). We restarted ETP and CBDCA chemotherapy, but the patient discontinued because he experienced delirium. At that time, the FoundationOne® genomic test on the biopsy specimen of the pelvic floor tumor diagnosed as NEPC revealed a *BRCA2* gene mutation and some variants of uncertain significance (Table S1). A single-site analysis with peripheral blood was performed to confirm the pathogenic variant identified in FoundationOne®; the patient harbored a *BRCA2* germline mutation. Therefore, olaparib was administered as a fifth-line treatment for prostate cancer. The proGRP level decreased, and the tumor diminished in size, indicating stable disease following the revised Response Evaluation Criteria in Solid Tumors version 1.1.[5] However, the proGRP level gradually increased after 1 year of treatment with olaparib and 15 months after initiating olaparib, the pelvic floor tumor showed regrowth, indicating progressive disease. The patient continued olaparib for 40 months after t-NEPC diagnosis because of a slow increase in tumor size and minimal side effects.

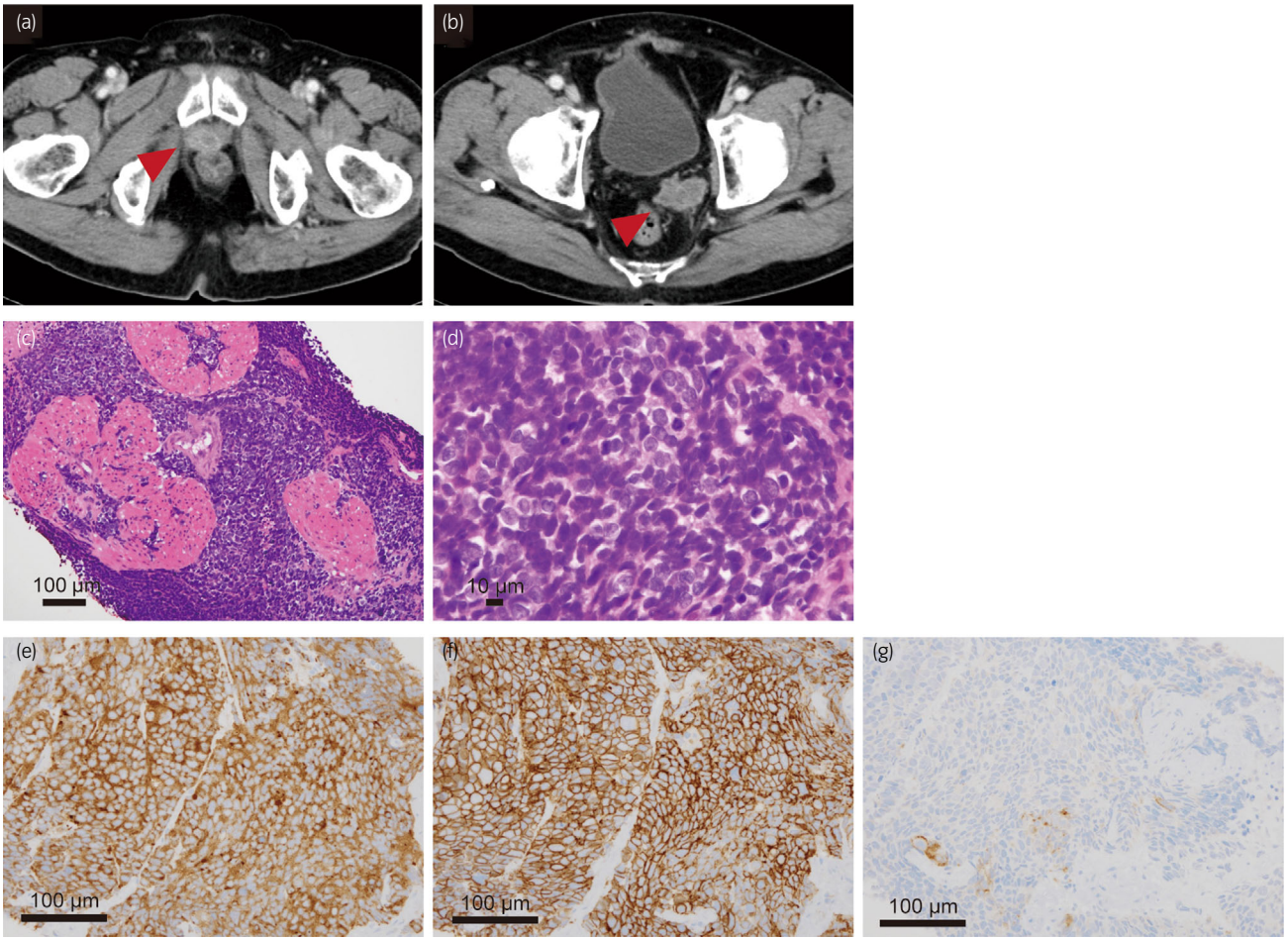

Fig. 1 Computed tomography image when the patient was diagnosed with t-NEPC (a, b) and microscopic findings of the tumor (c–g). (c) Small, clustered cells with a high nuclear-to-cytoplasmic ratio and no glandular pattern are observed (hematoxylin and eosin staining: ×20). (d) There are frequent mitotic figures (hematoxylin and eosin staining: ×100). (e) The tumor cells are positive for synaptophysin, (f) CD56, and (g) chromogranin A, partially (×200).

Discussion

To our knowledge, this is the eighth t-NEPC case treated with olaparib, and the rarity of our case is due to the relatively long-term disease control with olaparib. Low serum PSA levels, positive neuroendocrine markers, and an aggressive clinical course characterize t-NEPC.[3,6] Our patient experienced rapid local progression and distant lymph node metastasis with low PSA levels and was diagnosed with t-NEPC after a 10-year ADT. de novo NEPC at the initial diagnosis of prostate cancer is very rare;[7] however, the incidence of t-NEPC in CRPC is considered high because of the widely used ADT and androgen receptor axis-targeted agents.[8] Aggarwal *et al*. reported that 17% of patients with CRPC had histologic neuroendocrine features in biopsies of metastatic sites.[4]

In reports of t-NEPC genomic alteration, *MYCN* and *AURKA* amplifications were detected in 65% of patients with primary prostate cancer who developed t-NEPC.[9] Loss of function in *TP53* or *RB1* is not observed in a few t-NEPC cases.[10] These genomic features may be deeply involved in the development of t-NEPC;[3] however, we did not observe these gene mutations in our patient, indicating there might be other genomic or epigenetic alterations that trigger t-NEPC arising from initial adenocarcinoma.[11] t-NEPCs often present poorer prognosis than common prostate adenocarcinoma.[4] Following the National Comprehensive Cancer Network guidelines version 1.2023, the standard treatment for NEPC is chemotherapy with ETP and platinum-based drugs such as CDDP. t-NEPCs are initially sensitive to chemotherapy; tumors soon develop resistance, and median overall survival is approximately 7 months.[3,12] Therefore, more effective treatment options are required. Recently, several cases of t-NEPC treated with olaparib have been reported. The clinical features of seven previously reported cases and the present case are summarized in Table 1.[13–18] Three patients exhibited a partial response to olaparib. However, in most cases, the efficacy of olaparib in treating t-NEPC was observed only for a short duration (<6 months). In contrast, in our case, olaparib provided >1-year efficacy with stable t-NEPC. Regarding ovarian cancer, platinum resistance is related to olaparib resistance.[19] In our patient, platinum-based chemotherapy was

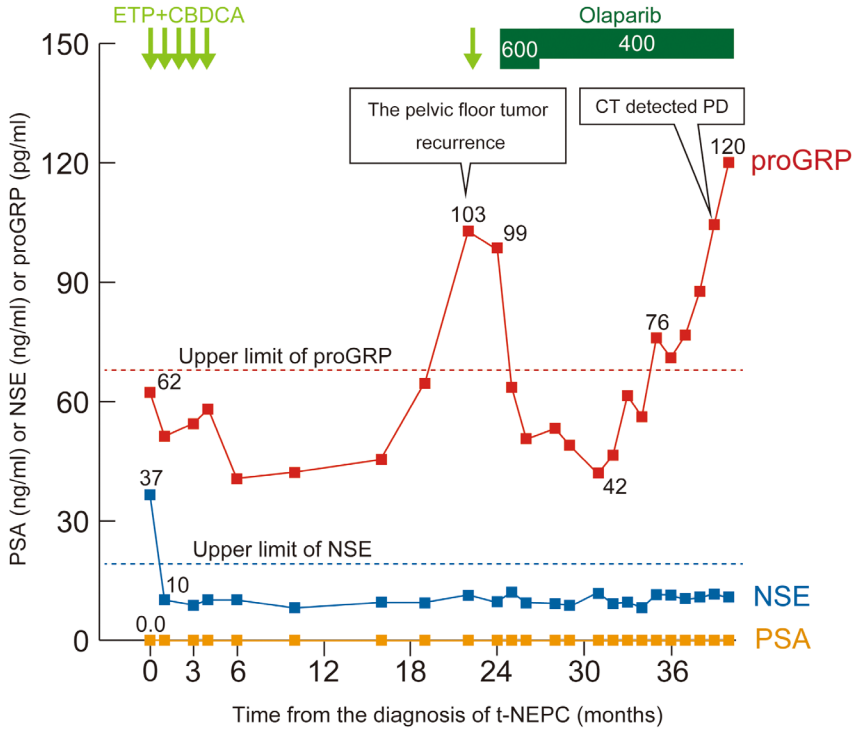

Fig. 2 The clinical course after the diagnosis of t-NEPC. Olaparib resulted in decreased proGRP level and tumor reduction.

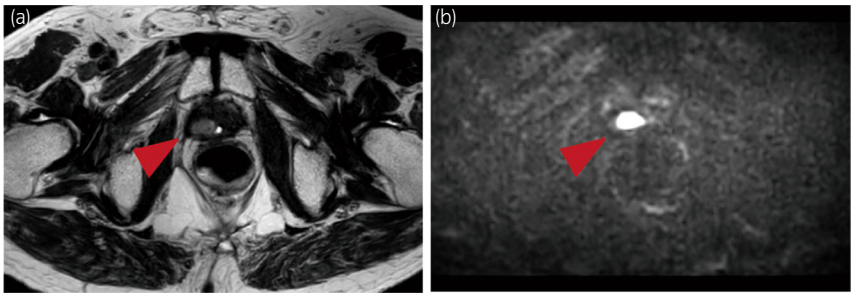

Fig. 3 Magnetic resonance imaging of recurrent pelvic floor tumor before olaparib administration. The tumors show faintly high signal intensity on T2-weighted images and are diffusion-weighted image-positive.

Table 1 Clinical features of t-NEPC cases treated with olaparib

		At the diagnosis of prostate adenocarcinoma						At the diagnosis of t-NEPC							
No.	Author	Age, year	PSA, ng/mL	Gleason score	Tumor stage	Treatment	Time to NEPC	PSA, ng/mL	NSE, ng/mL	proGRP, pg/mL	Sites of organ metastasis	*BRCA* mutation	Treatment	Outcome	Survival from NEPC diagnosis
1	Turina, *et al.* 2019[13]	N/A	9.23	4 + 4	pT3bN0	Local treatment: RP 1st line: ADT 2nd line: ENZ	73 week	9.93	N/A	N/A	Liver, bladder	*BRCA2* Copy number loss	1st line: ETP + CBDCA maintenance therapy: olaparib	NED	51 week
2	Wu *et al.* 2020[14]	63	55.13	4 + 4	cT4N1M1b	1st line: GOS + BCL 2nd line: ABI + BCL	7 month	1.5	212.9	976.2	Liver, lung	*BRCA1*	1st line: olaparib+RT 2nd line: ETP + CDDP	CD	5 month
3	Pandya *et al.* 2021[15]	65	95	4 + 4	M1b	LPR + ABI	16 month	0.5	824	N/A	Liver	*BRCA2* (Ser1882*)	1st line: ETP + CBDCA 2nd line: olaparib 3rd line: pembrolizumab 4th line: platinum-based chemotherapy	CD	18 month
4	Naiki *et al.* 2022[16]	63	20.3	4 + 3	cT2N1M1a	Surgical castration+ABI	10 month	N/A	27.4	N/A	Liver, bone	*BRCA2* (H1223fs*9)	1st line: ETP + CDDP 2nd line: amrubicin 3rd line: olaparib	CD	10 month
5	Miyazawa Y, *et al.* 2022–2 cases[17]	70	40.8	4 + 5	cT3bN1M1b	CAB+RT(prostate)	36 month	<0.01	171	N/A	Liver, bone	*BRCA2*	1st line: ETP + CDDP 2nd line: ENZ 3rd line: olaparib	AWD	N/A
6		78	15.2	4 + 4	cT3bN0M0	Local treatment: RP 1st line: ADT 2nd line: BCL 3rd line: ENZ 4th line: DTX 5th line: CBZ	N/A	N/A	N/A	N/A	Bladder	*BRCA2*	1st line: ETP + CBDCA 2nd line: olaparib	AWD	N/A
7	Kaitsumaru M, *et al.* 2023[18]	67	29.99	5 + 5	M1b	1st line: LPR + ENZ 2nd line: DTX	20 month	0.19	211	53.5	Liver, bone	*BRCA1* (deletion of intron 3–7)	1st line: olaparib	CD	6 month
8	The present case	64	6.5	4 + 5	cT3N0M0	Local treatment: RP 1st line: ADT 2nd line: salvage RT	132 month	0.001	31.8	65.8	None	*BRCA2* (D427fs*3)	1st line: ETP + CBDCA 2nd line: olaparib	AWD	40 month

still effective, and olaparib was initiated before the tumor acquired platinum resistance. This suggests that olaparib can be successfully used to treat t-NEPC before chemotherapy or as an early-line treatment.

Conclusion

We report a case of t-NEPC treated with olaparib that achieved a 1-year stable disease. Additional cases are required to clarify the ideal treatment strategy for t-NEPC; however, olaparib may be the treatment of choice for this aggressive disease.

Acknowledgments

We would like to thank Editage (www.editage.com) for the English language editing.

Author contributions

Riko Ikeda: Writing – original draft. Yoh Matsuoka: Supervision; writing – review and editing. Masaharu Inoue: Supervision. Ayataka Ishikawa: Supervision. Kiwamu Akagi: Supervision. Yukio Kageyama: Supervision.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

Informed consent

Informed consent was obtained from the patient. using the opt-out method. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079702/).

Registry and the Registration No. of the study/trial

Not applicable.

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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. Gene alterations in our case.