Case Report

A case of double-negative prostate cancer with *BRCA2* mutation and high tumor mutation burden treated sequentially with olaparib and pembrolizumab

Hiroki Tanaka,[1] Soichiro Yoshida,[1] Satoru Aoyama,[2] Sadakatsu Ikeda,[2] Junko Kunieda,[3] Kenichi Ohashi,[3] Shohei Fukuda,[1] Yuma Waseda,[1] Hajime Tanaka[1] and Yasuhisa Fujii[1]

Departments of [1]Urology, [2]Precision Cancer Medicine, and [3]Pathology, Tokyo Medical and Dental University, Tokyo, Japan

Abbreviations & Acronyms
AR = androgen receptor
ARSI = AR signaling inhibitor
CT = computed tomography
CTCAE = Common Terminology Criteria for Adverse Events
DNPC = double-negative prostate cancer
HE = hematoxylin and eosin
mCRPC = metastatic castration-resistant prostate cancer
MET-RADS-P = METastasis Reporting and Data System for Prostate Cancer
MRI = magnetic resonance imaging
NSE = neuron-specific enolase
OS = overall survival
PARP = poly ADP-ribose polymerase
PCa = prostate cancer
PD-L1 = programmed death-ligand 1
PFS = progression-free survival
ProGRP = pro-gastrin-releasing peptide
PSA = prostate-specific antigen
RAC = response assessment category
TMB = tumor mutational burden
tTMB-high = high tissue tumor mutational burden
TUR = transurethral resection
WB-DWI = whole-body diffusion-weighted magnetic resonance imaging

Correspondence: Soichiro Yoshida M.D., Ph.D., Department of Urology, Tokyo Medical and Dental University Graduate School, 1-5-45 Yushima, Bunkyo-Ku, Tokyo 113–8510, Japan. Email: s-yoshida.uro@tmd.ac.jp

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Introduction: Double-negative prostate cancer, an androgen receptor–independent prostate cancer without features of neuroendocrine tumors, is refractory to treatment but could be an ideal candidate for individualized treatment.
Case presentation: An 85-year-old patient with metastatic castration-resistant prostate cancer without prostate-specific antigen progression presented with local recurrence and liver and lung metastases 6 months after orchiectomy and apalutamide. A liver tumor biopsy led to a diagnosis of double-negative prostate cancer. FoundationOne® CDx showed *BRCA2* mutation and high tumor mutation burden. Olaparib and pembrolizumab were administered sequentially, and the patient responded to each treatment for 5 months until radiographic progression.
Conclusion: Sequential use of olaparib and pembrolizumab may be effective for double-negative prostate cancer with *BRCA2* mutations and high tumor mutation burden.

Key words: androgen receptor antagonists, diffusion magnetic resonance imaging, DNA mutational analysis, genes, BRCA2, prostatic neoplasms, castration-resistant.

Keynote message

Double-negative prostate cancer can progress without PSA progression. Sequential use of olaparib and pembrolizumab may be effective for double-negative prostate cancer in cases with *BRCA2* mutations and high tumor mutation burden. Whole-body diffusion-weighted imaging was effective in assessing lesion size over time for double-negative prostate cancer.

Introduction

The efficacy of PARP inhibitors has been demonstrated in mCRPC with *BRCA1/2* mutations.[1,2] tTMB-high has been correlated with the induction of neoantigens and a favorable therapeutic response to pembrolizumab in patients with tTMB-high solid malignancies.[3] DNPC is an AR–independent PCa without features of neuroendocrine tumors refractory to treatment but could be an ideal candidate for individualized treatment.[4] Here, we report a case of DNPC characterized as *BRCA2* mutation-positive and tTMB-high that was treated sequentially with olaparib and pembrolizumab. Disease status was monitored using WB-DWI, and treatment response was assessed according to MET-RADS-P, recommended for WB-DWI interpretation.[5]

Case

The patient, an 85-year-old man, underwent left nephroureterectomy for left ureteral cancer in 1991. In 2011, a prostate biopsy revealed prostate cancer cT1cN0M0, Gleason grade group 3 at a serum PSA level of 8.55 ng/mL. External beam radiation therapy (70 Gy/35 Fr) was performed, and the patient's PSA nadir was 0.86 ng/mL in 2013. His PSA level in 2020 was 1.512 ng/mL, but he did not visit our outpatient clinic after that and was followed by his local doctor. In 2022, his PSA level increased to 4.04 ng/mL and he visited our hospital

again. WB-DWI was performed, and the patient was diagnosed with locally recurrent PCa invading the bladder and left pelvic floor, with metastases to the liver and lungs. Transurethral tumor resection was performed due to bleeding from a tumor in the bladder neck, which was histopathologically diagnosed as bladder invasion of PCa. Bilateral orchiectomy was performed concurrently. The patient developed postrenal acute renal failure (serum creatinine level of 4.87 mg/dL) due to right hydronephrosis caused by the bladder-neck invasion of PCa. A right nephrostomy tube was placed, and serum creatinine declined to 1.23 mg/dL. Treatment with apalutamide 120 mg/day was started, and after 4 months, the patient's PSA level decreased to 0.006 ng/mL (Fig. 1). The treatment response, as defined by MET-RADS-P, was categorized as RAC 2, indicating "likely to be responding." However, due to a skin rash (Grade 2 per CTCAE v5.0), apalutamide was discontinued. In the following month, PSA was 0.006 ng/mL; however, WB-DWI demonstrated enlargement of liver metastases (RAC 5: highly likely to be progressing) and lung metastases (RAC 4: likely to be progressing). A biopsy of the liver metastases was performed and showed a structure similar to that of the PCa tissue from the biopsy at diagnosis. The tissue was partially positive for NKX3.1 on immunostaining, but negative for PSA, chromogranin A, and synaptophysin (Fig. 2). Serum NSE and proGRP levels were within normal limits. The patient was diagnosed with DNPC. The patient did not hope to receive docetaxel for mCRPC, and treatment with enzalutamide 80 mg/day was initiated. However, WB-DWI performed 3 months later showed local recurrence; in addition, the liver and lung metastases had progressed and the metastasis of a large left internal iliac lymph node appeared (RAC 5). The FoundationOne® CDx diagnostic test using TUR specimen showed a somatic *BRCA2* mutation (rearrangement of intron 2), TMB-high (10 Muts/Mb), an *RB1* inactivating mutation, and a *TP53* defect. Treatment with olaparib started at a reduced dose of 400 mg/day due to chronic kidney disease. After 2 months, local recurrence and liver and lung metastases had shrunk (RAC 2). Three months later, WB-DWI demonstrated that the liver and lung metastases remained small (RAC 1: highly likely to be responding). However, further local recurrent disease and invasion of the rectovesical pouch were observed (RAC 5) accompanied by symptoms of constipation due to anal stenosis (Fig. 3). The patient was then treated with pembrolizumab 200 mg every 3 weeks. After 3 cycles, a reduction in local recurrence and liver and lung metastases was observed on WB-DWI (RAC 1). After 5 months of pembrolizumab treatment (7 cycles), the patient had a serum PSA level of 0.048 ng/mL. The liver and lung metastases remained stable (RAC 1), but local

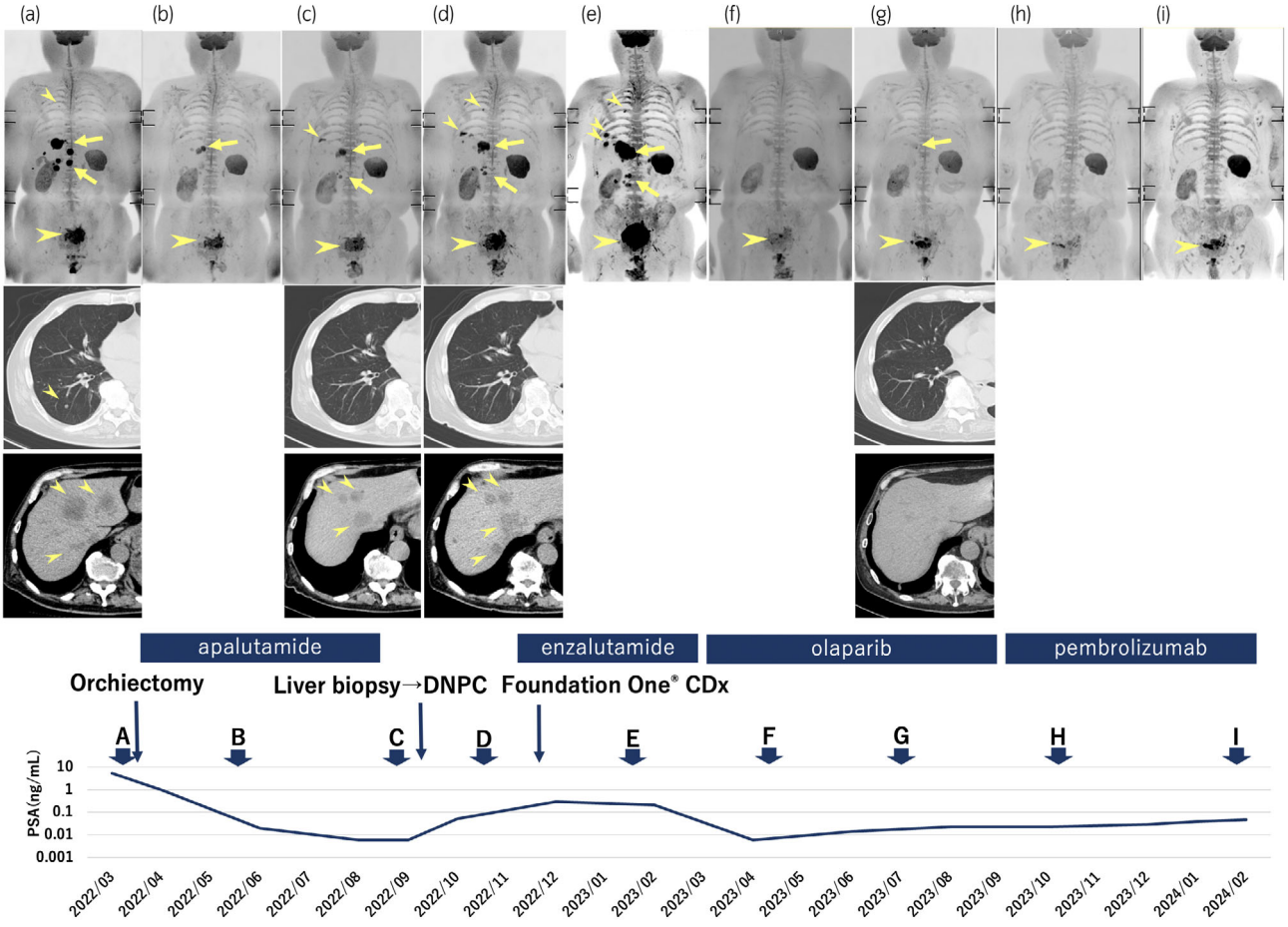

Fig. 1 Treatment course, trends of serum PSA levels, and corresponding WB-DWI and CT images (a–i).

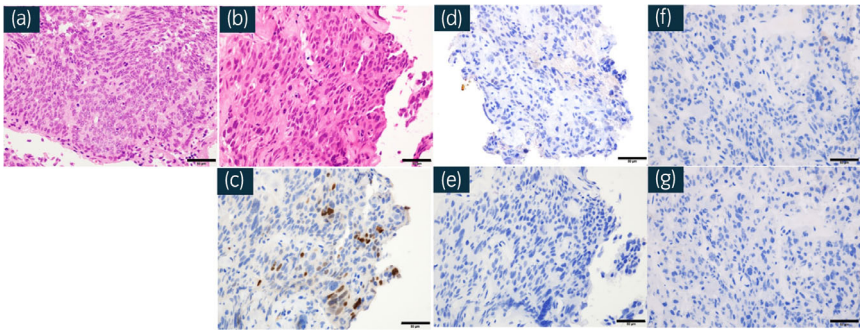

Fig. 2 Pathological findings of the PCa and liver metastases. (a) HE staining of prostate biopsy specimen; (b) HE staining of liver metastases; and (c) immunostaining of NKX3.1 (positive). Immunostaining of AR (d), PSA (e), chromogranin A (f), and synaptophysin (g) was negative. Scale bar: 50 μm.

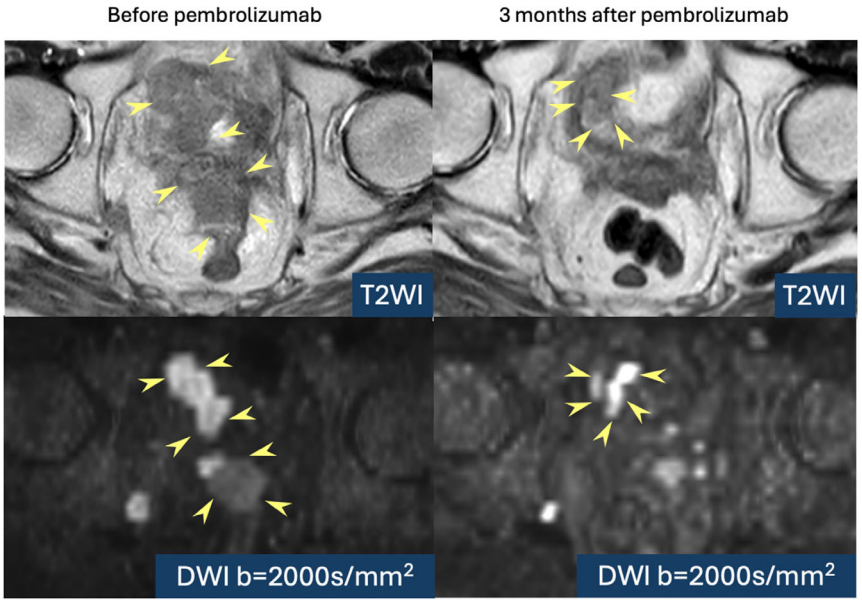

Fig. 3 T2-weighted and diffusion-weighted MRI before and 3 months after pembrolizumab treatment. Invasion of the rectovesical pouch in the local lesion was reduced and rectal stenosis improved.

recurrence and infiltration into the rectal fossa were observed again (RAC 5).

Discussion

ARSI may induce AR-independent PCa.[5] DNPC accounts for 20% to 25% of mCRPC.[5,6] The incidence of *BRCA* mutations does not differ between AR-dependent PCa, neuroendocrine PCa, and DNPC.[6] In this case, DNPC was likely induced by apalutamide, and subsequent treatment with enzalutamide had no therapeutic effect. *RB1* mutations are significantly more prevalent in AR-independent PCa than in AR-dependent PCa and are associated with shorter survival in CRPC.[7–9]

In our patient, radiological PFS with olaparib was 5 months, slightly shorter than the 7.4 months reported in the PROfound trial showing olaparib efficacy in metastatic CPRC positive for *BRCA1/2* or *ATM* mutations.[1,2] Sequential pembrolizumab showed a good therapeutic response for 2 months. Increased neoantigen release by PARP inhibitors may increase responsiveness to immunotherapy via increased TMB and PD-L1 expression.[6] However, a prospective study showed that pembrolizumab plus olaparib did not significantly prolong OS or radiological PFS in biomarker-unselected mCRPC.[7] Future studies are needed to discuss whether PARP inhibitors or pembrolizumab should be given first to PCa patients with high tumor mutation burden who have BRCA2 mutations.

The utility of MRI in monitoring tumor activity in bone metastases and MRI evaluation is recommended.[8,9] Routine imaging assessment is important in DNPC and neuroendocrine cancer because the PSA level alone may not accurately reflect disease status.[10] In this DNPC case, evaluating signal changes over time using a combination of CT and WB-DWI, in the absence of PSA progression, facilitated an accurate disease status assessment. Thus, imaging assessment can significantly impact treatment strategy.

Conclusions

Sequential use of olaparib and pembrolizumab may be effective for DNPC in cases characterized by *BRCA2* mutations and high tumor mutation burden. WB-DWI is effective in assessing lesion size over time and in guiding treatment strategy.

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Author contributions

Hiroki Tanaka: Visualization; writing – original draft. Soichiro Yoshida: Conceptualization; project administration; supervision; writing – review and editing. Satoru Aoyama: Resources. Sadakatsu Ikeda: Resources; writing – review and editing. Junko Kunieda: Resources; writing – review and editing. Kenichi Ohashi: Resources; writing – review and editing. Shohei Fukuda: Writing – review and editing. Yuma Waseda: Writing – review and editing. Hajime Tanaka: Writing – review and editing. Yasuhisa Fujii: Supervision; writing – review and editing.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

Informed consent

Written informed consent was obtained from the patient.

Registry and the Registration No. of the study/trial

Not applicable.

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