Effect of cisplatin on metastatic castration-resistant prostate cancer with BRCA2 mutation: A case report

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ABSTRACT
Poly (ADP-ribose) polymerase inhibitors exhibit strong activity for treating the DNA damage repair defect in patients with prostate carcinoma (PCa). Although conventional DNA-damaging agents can theoretically lead to synthetic antitumoral effects, no report has clearly mentioned the clinical use of cisplatin for treating PCa patients with the breast cancer gene (BRCA)2 mutation. We administered 80 mg/m² cisplatin triweekly to a patient with metastatic castration-resistant PCa (mCRPC) with the BRCA2 mutation, and after ten cycles, the prostate-specific antigen was dramatically decreased. We suggest that BRCA2 mutations may indicate the use of cisplatin for treating patients with mCRPC.

Introduction
Genetic analysis of the DNA damage repair defect (DDRD) in prostate carcinoma (PCa) has been highlighted in precision medicine for patients with metastatic castration-resistant PCa (mCRPC). Poly (ADP-ribose) polymerase (PARP) facilitates DNA repair, and PARP inhibitors (PARPi) strengthen the activity in patients with the DDRd, especially in those with breast cancer gene (BRCA) mutations. Both PARPi and conventional DNA-damaging agents can theoretically exert synthetic antitumoral effects, and cisplatin may be a potential chemotherapeutic agent for mCRPC. Although DDRd mutations occur in 20%–30% of patients with advanced PCa, no report has clearly mentioned cisplatin’s clinical use in PCa patients with BRCA mutations. Here, we describe a first case of cisplatin administration in an mCRPC patient with the BRCA2 mutation.

Case presentation
A 37-year old man with PCa (cT2bN0M0, Gleason score 3 + 4, adenocarcinoma and initial prostate-specific antigen [PSA]: 28.5 ng/ml) underwent a robot-assisted laparoscopic prostatectomy with bilateral pelvic lymphadenectomy. This patient had a family history of malignancy; his mother was diagnosed with breast cancer in her 50s. The final pathology showed Gleason 4 + 5 and PCa with pT3bN0 with negative resection margins. The postoperative PSA had a nadir of 5.61 ng/ml at 3 months postsurgery and reached 9.93 ng/ml 2 months after the nadir. Bicalutamide and salvage radiation therapy (SRT) for the prostatic fossa (66 Gy) were introduced. Twenty-five months later, the PSA had decreased to 1.37 ng/ml, then gradually rose to 11.0 ng/ml despite the addition of leuprorelin acetate followed by abiraterone for the castration resistance and SRT for left internal iliac lymph node metastasis (60 Gy) and bone metastasis in the second thoracic vertebra (Th2) (30 Gy). The patient underwent 19 courses of docetaxel (60 mg/m²) and five courses of cabazitaxel (25 mg/m²) thereafter. Docetaxel reduced the PSA by 85%; however, cabazitaxel induced no PSA response. After the disease progressed while the patient underwent taxane-based chemotherapy, we performed a genetic test by FoundationOne CDx® using surgical specimens to determine the next therapeutic drug. Genetic testing revealed a frameshift mutation with a stop codon two positions further in the BRCA2 (pA902fs*2); however, no PARPi had yet been approved in Japan. Thus, we administered cisplatin, the only platinum drug approved to treat PCa in Japan, at 80 mg/m² triweekly. We also administered SRT to the L4 (20 Gy) and Th11/12 (30 Gy) vertebrae to relieve the backache and numbness in the patient’s legs, respectively. Thereafter, the PSA continued to decrease from 158.7 ng/ml to 27.7 ng/ml over the course of ten cycles of cisplatin (Fig. 1), with the...
improvement of the spinal cord compression of Th11/12 (Fig. 2).

Discussion

Platinum compounds exert their antitumoral effects by forming covalent DNA adducts that result in DNA damage (G2 phase). In ovarian and breast cancer, patients with BRCA mutations have exhibited high sensitivity to platinum agents. In advanced triple-negative breast cancer with BRCA1/2 mutations, carboplatin had twice the objective response rate of docetaxel (68% vs 33%, \( P = 0.01 \)), whereas no significant differences were noted in unselected patients between the two treatment groups.

Regarding PCa, limited data show encouraging PSA response rates to platinum-based chemotherapy in mCRPC patients with BRCA2 mutations despite their resistance to prior standard treatments. A retrospective study investigated the therapeutic differences in a combination therapy of carboplatin and docetaxel between mCRPC patients with and without the BRCA2 mutation. The PSA decreased by 50% (PSA50) in 6 of 8 patients (75%) with the mutation and in 23 of 133 patients (17%) without the mutation (\( P < 0.001 \)). Schmid et al. also found a high response in patients with the BRCA2 mutation in a large retrospective study that included 80 CRPC patients with DDRd. Platinum-based chemotherapy yielded a PSA50 in 63.9% of patients (23/44) with the BRCA2 mutation. Additionally, among some DDRd types, patients with the BRCA2 mutation had a significantly better median overall survival than did those with other aberrations (BRCA2: 15.2 months, Ataxia telangiectasia mutated (ATM): 9.3 months, BRCA1: 4.1 months, \( P = 0.04 \)). However, these promising results were mostly attributed to carboplatin-based chemotherapy. To our knowledge, only one case with a DDRd underwent cisplatin monotherapy, and the aberration type and treatment outcome were not described in detail. Cisplatin is thought to have similar antitumoral effects to those of carboplatin, and the treatment choice of cisplatin or carboplatin usually depends on the specific toxicity.

Here, cisplatin was administered as the 4th line therapy for mCRPC owing to the lack of approval of PARPi. However, olaparib is currently approved in Japan, raising the question of whether sequential treatments with PARPi and platinum-based chemotherapy can be used to treat mCRPC with BRCA mutations. A phase 3 clinical trial (SOLO2) for patients with platinum-sensitive, relapsed ovarian cancer with BRCA1/2 mutations showed that olaparib significantly prolonged progression-free survival. Conversely, large clinical trials for PARPi for mCRPC, including the PROfound and TOPARP-B trials, excluded patients who had previously received platinum-based chemotherapy. A review focusing on PCa patients treated with both carboplatin agents and PARPi revealed that PSA50 occurred only when carboplatin was administered first, followed by PARPi, whereas the reverse sequence diminished the efficacy of the subsequent carboplatin. However, because the number of patients with DDRd in this report was small, more patients are needed in future prospective clinical trials to verify these results.

One limitation of our case study is that the SRT for the L4 and TH11/12 vertebrae may have affected the PSA decrease after cisplatin use. However, the tumor characteristics presented in our case seemed to be insensitive to the SRT, especially after the castration resistance, and the PSA continued to increase even after SRT for Th2. Thus, we believe that administering cisplatin significantly decreased the PSA.

Conclusion

This case suggests potential predictive role of BRCA2 mutation for cisplatin in patients with mCRPC. We hope that genetic analysis in further large prospective studies will contribute to new individual strategies for treating mCRPC.

Ethical considerations

Informed consent for this case report including medical images was obtained from the patient.
Declaration of competing interest

There are no conflicts of interest or funding to report.

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