Case Report

Validity of Weekly Administration of Carboplatin after Carboplatin-Induced SIADH: Two Case Reports and Literature Review

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Keywords

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Abstract

Chemotherapy-induced severe hyponatremia is a life-threatening condition. Platinum-based agents play a key role in ovarian cancer treatment but are more likely to cause hyponatremia than other anticancer agents. The optimal strategy for treating ovarian cancer in cases of severe platinum agent-induced hyponatremia remains unclear. We encountered 2 patients with ovarian cancer who developed syndrome of inappropriate antidiuretic hormone secretion (SIADH) after chemotherapy with involved carboplatin. Case 1 was a recurrent ovarian clear-cell carcinoma with peritoneal dissemination, and the patient developed severe hyponatremia due to SIADH on day 5 after receiving triweekly docetaxel and carboplatin (DC) therapy. The chemotherapy regimen was changed to weekly DC therapy, and she completed six cycles of regimen without electrolyte disturbance or tumor recurrence. Case 2 was a newly diagnosed advanced high-grade serous ovarian carcinoma, stage IIIC, with a BRCA1 mutation. She developed SIADH on day 8 after receiving triweekly paclitaxel and carboplatin (TC) therapy as adjuvant therapy after primary debulking surgery. The regimen was changed to weekly TC therapy, and she completed the schedule of chemotherapy without electrolyte disturbance and transitioned to maintenance therapy with a PARP inhibitor. In conclusion, weekly carboplatin administration might be a promising alternative to triweekly carboplatin administration after the development of carboplatin-induced SIADH.

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Introduction

Hyponatremia occurs in 2.6–29.1% of patients receiving chemotherapy [1]. Although platinum-based agents play a key role in ovarian cancer treatment, they are more likely to cause hyponatremia than non-platinum-based agents (incidence of hyponatremia: 11.9% and 3.8%, respectively) [1]. In previous reports, platinum-based drugs were often replaced with non-platinum-based drugs, other platinum-based drugs, or they were discontinued due to severe drug-induced hyponatremia [2, 3]; however, the optimal strategy is still unknown. Here, we report 2 cases of severe hyponatremia due to SIADH after triweekly carboplatin administration for the treatment of ovarian cancer. We changed the regimen to weekly administration by dividing the dose of carboplatin, and no hyponatremia occurred despite not changing the drug type.

Case Report/Case Presentation

Case 1

A 77-year-old woman underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, and pelvic and para-aortic lymphadenectomy for the treatment of right ovarian cancer. The postoperative diagnosis was right ovarian clear-cell carcinoma (stage IC3). She received adjuvant chemotherapy with weekly paclitaxel (75 mg/m²) and carboplatin (area under the curve [AUC]: 2) on days 1, 8, and 15. On day 8, the regimen was discontinued because of elevated serum liver enzyme levels due to paclitaxel-induced liver injury. The regimen was modified to irinotecan (60 mg/m² on days 1, 8, and 15) and cisplatin (60 mg/m² on day 1). However, on day 6, she experienced convulsions and hyponatremia (serum sodium level: 109 mEq/L) without a diagnosis of SIADH at this time. She was treated with supplemental sodium chloride, and her sodium level recovered 6 days after the onset of convulsions. Hence, the patient was followed up without adjuvant chemotherapy. Five years and 8 months after the surgery, the patient's cancer antigen 125 (CA125) level was elevated to 569 U/L, and positron emission tomography/computed tomography showed multiple peritoneal dissemination, indicating recurrence of ovarian cancer (Fig. 1). She received chemotherapy with docetaxel (70 mg/m² on day 1), carboplatin (AUC: 6 on day 1), and bevacizumab (15 mg/kg on day 1) due to her history of liver injury and hyponatremia following

Fig. 1. a, b Positron emission tomography/computed tomography image showing multiple peritoneal dissemination of recurrent ovarian cancer (white arrows).

Fig. 2. **a** Serum sodium level and sodium supplementation in case 1. **b** Serum sodium level and sodium supplementation in case 2.

paclitaxel and cisplatin administration, respectively. On day 5, the patient complained of general malaise. Hematological examination revealed a serum sodium level of 115 mEq/L, antidiuretic hormone level of 7.5 pg/mL, creatinine level of 0.52 mg/dL, and cortisol level of 31.5 µg/dL, with a plasma osmolality of 236 mOsm/kg and urine osmolality of 631 mOsm/kg. Physical examination did not reveal any symptoms of hypovolemia or hypervolemia. She was diagnosed with carboplatin-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH) and treated with hypertonic saline infusion. Her serum sodium level gradually increased to normal levels 8 days after sodium supplementation (Fig. 2a). Although SIADH occurred, the CA125 level was reduced to 66 U/L, demonstrating the efficacy of the regimen. The patient received chemotherapy with divided doses of docetaxel (35 mg/m² on days 1, 8, and 15) and

carboplatin (AUC: 2 on days 1, 8, and 15), for which she provided informed consent. After weekly administration of docetaxel and carboplatin (weekly DC), her CA125 levels further decreased to normal levels. She completed six cycles of weekly DC without electrolyte disturbance or tumor recurrence.

Case 2

A 78-year-old woman with abdominal distension was suspected to have ovarian cancer and was referred to our hospital for treatment. Her medical history included thyroid cancer after thyroidectomy and bilateral breast cancer after mastectomy. Pelvic MRI revealed a solid tumor in the Douglas pouch involving the rectum, and abdominal CT revealed para-aortic lymph node swelling and omental cake. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, low anterior rectum resection, and para-aortic lymphadenectomy were performed for primary debulking surgery.

Twenty-three days after surgery, she received adjuvant chemotherapy with paclitaxel (175 mg/m²) and carboplatin (AUC: 6). On day 8, she experienced dizziness, nausea, and vomiting. Hematological examination revealed a serum sodium level of 114 mEq/L, antidiuretic hormone level of 5.3 pg/mL, creatinine level of 0.52 mg/dL, and cortisol level of 22.7 µg/dL, with a plasma osmolality of 231 mOsm/kg and urine osmolality of 352 mOsm/kg. The excretion of sodium level (90 meq/L) was elevated. Physical examination did not reveal any hypovolemia. She was diagnosed with carboplatin-induced SIADH and was treated with hypertonic saline infusion and supplemental sodium chloride. Her sodium level recovered 6 days after the onset of dizziness (Fig. 2b). The patient received chemotherapy with divided doses of paclitaxel (75 mg/m² on days 1, 8, and 15) and carboplatin (AUC: 2 on days 1, 8, and 15), for which she provided informed consent. She completed five cycles of weekly paclitaxel and carboplatin (TC) therapy without electrolyte disturbance or tumor recurrence and successfully transitioned to olaparib maintenance therapy as a BRCA1 mutation carrier.

Discussion/Conclusion

The main causes of severe hyponatremia after administration of platinum-based agents are SIADH and renal salt wasting syndrome (RSWS). SIADH is a disorder of impaired water excretion due to the oversecretion of ADH from the posterior pituitary. The treatment included fluid restriction and sodium supplementation. The occurrence of SIADH has been associated with ectopic ADH-producing tumors, lung disease, surgical stress, central nervous system disease, and the use of certain medications, as was the case here [4]. In RSWS, impaired proximal tubular reabsorption of sodium and water induces hyponatremia and dehydration, which is often caused by platinum-based agents. The treatment of RSWS includes fluid replacement. Differential diagnosis is difficult but important because the treatment strategy differs [5]. SIADH was diagnosed on the basis of severe hyponatremia, hypo-osmolality, high urine osmolality and urinary sodium level, and clinical euvoemia. Our cases did not have dehydration or renal dysfunction, which indicated that the hyponatremia was caused by SIADH and not by RSWS. Ezoe et al. [1] reported that cisplatin caused hyponatremia more often than carboplatin; the incidence of grade 3/4 hyponatremia was 13.5% in patients treated with cisplatin and 7.6% in those treated with carboplatin. They attributed this difference to nephrotoxicity due to the mechanism of cisplatin excretion [6]. Only 5 cases of hyponatremia after carboplatin administration have been reported; among them, 1 patient had RSWS [7], and the other four had SIADH [2, 3, 8, 9]. While RSWS is a common cause of cisplatin-induced hyponatremia [10], SIADH is the most

Table 1. Reports of carboplatin-induced syndrome of SIADH

Reporter	Age/sex	Tumor type	Chemotherapy regimen	Nadir serum sodium level, mEq/L	Next treatment for tumor
Fujioka et al. [8]	60/F	Lung cancer	CBDCA+PTX	101	No record
Yokoyama et al. [2]	63/F	Ovarian cancer	CBDCA+PTX	109	CDDP+PTX
Turner et al. [3]	49/F	Breast cancer	CBDCA+DTX+HER	105	DTX+HER (without CBDCA)
Sugiyama et al. [9]	66/F	Urethral cancer	CBDCA+PTX	No record	Continued (SIADH was controllable)
Our case 1	77/F	Ovarian cancer	CBDCA+DTX+BEV	115	CBDCA+DTX (weekly regimen)
Our case 2	78/F	Ovarian cancer	CBDCA+PTX	114	CBDCA+PTX (weekly regimen)

CBDCA, carboplatin; PTX, paclitaxel; CDDP, cisplatin; DTX, docetaxel; HER, trastuzumab; SIADH, syndrome of inappropriate antidiuretic hormone secretion; BEV, bevacizumab.

common cause of carboplatin-induced hyponatremia. In our cases, grade 4 hyponatremia occurred after the administration of taxane drugs and carboplatin. Hyponatremia is more likely caused by the administration of carboplatin (AUC: 6) because taxane drugs very rarely induce hyponatremia [11]. The ideal chemotherapy strategy after the development of carboplatin-induced SIADH has not been determined. We have listed the previous reports on carboplatin-induced SIADH in Table 1. Carboplatin administration was continued in only 1 of 4 patients who developed carboplatin-induced SIADH [9]. The patient in whom carboplatin administration was continued had grade 3 hyponatremia, which recovered following oral sodium supplementation, and chemotherapy was discontinued after two cycles because the regimen was not effective [9]. In the other 3 cases, the drug was changed or discontinued [2, 3]. Thus far, there have been no reports on the administration of a divided dose of carboplatin after the development of SIADH. The mechanism of SIADH prevention by reducing the dose is still unknown. We speculate that the reduction of stress on the hypothalamus by dividing the dose of carboplatin could reduce the risk of SIADH. Carboplatin is the most important drug for the treatment of ovarian cancer. Fortunately, the validity of divided doses of carboplatin had been shown in several studies [12, 13], which enabled us to divide the dose of carboplatin without hesitation after patients developed SIADH.

We administered a divided dose of carboplatin, which was found to be effective without reducing the total dose of carboplatin. Recurrent ovarian clear-cell carcinoma is generally resistant to chemotherapy [14]; therefore, it is important to avoid discontinuing the use of effective drugs, as shown in case 1. It is also important to complete the schedule of adjuvant chemotherapy for advanced ovarian cancer before initiating PARP maintenance therapy for BRCA carriers, as shown in case 2 [15].

Conclusion

Based on our experience, weekly carboplatin administration could be a promising alternative to triweekly carboplatin administration after the development of carboplatin-induced SIADH in patients with ovarian cancer.

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Statement of Ethics

We reported this case report in compliance with the Helsinki Declaration. This study protocol was reviewed, and the need for approval was waived by the Ethics Committee of Shizuoka General Hospital. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.F. drafted the manuscript. N.H. contributed to the conception and critical revision of the manuscript. T.Y., S.Y., R.K., M.T., M.U., R.G., and Y.I. participated in the clinical treatment. H.T. and K.K. reviewed the manuscript. All the authors approved the final version to be published and agreed to act as guarantors of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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