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Successful Management of Platinum-resistant Ovarian Cancer by Weekly Nedaplatin Followed by Olaparib: Three Case Reports

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Abstract. *Background: Treatment for platinum-resistant ovarian cancer is difficult and challenging because available chemotherapeutic agents only offer short survival improvements. The efficacy of re-treatment with platinum-based agents including nedaplatin for platinum-resistant patients has not been fully investigated. Case Report: We describe herein three cases of heavily treated platinum-resistant ovarian cancer that were successfully treated with weekly nedaplatin followed by olaparib. After becoming platinum-resistant, the cases were treated with non-platinum chemotherapies. Following these regimens, weekly nedaplatin was introduced, followed by olaparib. At the time of writing, survival since the start of weekly nedaplatin was 30 months for case 1, 20 months for case 2, and 17 months for case 3, with all patients showing no evidence of disease. Conclusion: Weekly nedaplatin followed by olaparib might represent a good treatment option for platinum-resistant ovarian cancer and is a solid candidate for further evaluation.*

More than 70% of patients with ovarian cancer are diagnosed at an advanced stage and undergo surgery and front-line combination chemotherapy. Among those, front-line chemotherapy using platinum-based agents with taxane is effective for 70-80% of patients, with about half of these achieving complete clinical remission (1-3). However, many patients experience relapse, and in most the disease is not curable, so consecutive treatments are needed. The platinum-free interval appears to be a critical factor in determining the response to salvage chemotherapy (4). Patients with a platinum-free interval of >6 months are considered platinum-sensitive (4). Disease in patients who do not show response to initial platinum therapy or who have relapse ≤6 months after completion of therapy is considered platinum-resistant (4). Platinum-based combination regimens are effective for patients with platinum-sensitive ovarian cancer, some of whom achieve prolonged survival. Olaparib is a poly (ADP-ribose) polymerase inhibitor that has been approved as a maintenance monotherapy for platinum-sensitive, and recurrent ovarian cancer (5). While treatment strategies for patients with platinum-sensitive cancer have improved, options for those with platinum-resistant disease remain limited. Non-platinum single-agent chemotherapies including pegylated liposomal doxorubicin (PLD) (6, 7), gemcitabine (8, 9), topotecan (10), oral etoposide (11) and weekly paclitaxel (12) are sequentially used for these patients. However, response rates to these agents are reportedly about 6-15% and progression-free survival under these regimens is only around 4 months (13). Furthermore, the addition of bevacizumab to these non-platinum regimens reportedly improves progression-free survival to a median of 6.7 months and increases the response rate (14). However, this progression-free survival is still unsatisfactory and investigation of new treatment strategies is warranted.

Among the strategies for the treatment of patients with platinum-resistant disease, re-treatment with platinum-based agents has been reported in some articles (15-19). The definition of platinum sensitivity has been considered somewhat arbitrary and is dependent on the timing of the diagnosis of recurrence (4). Kavanagh *et al*. reported a 21% response to platinum retreatment in patients with platinum-

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resistant ovarian cancer (15). Various platinum agents are available, but the type of platinum to be used in platinum retreatment of platinum-resistant ovarian cancer has yet to be elucidated. Moreover, whether the success of platinum retreatment can be considered as indicating platinum sensitivity has not been clarified. In Japan, nedaplatin has been approved for the treatment of ovarian cancer, and our Department has used weekly nedaplatin for recurrent ovarian cancer. In this article, we describe three patients who were successfully treated using weekly nedaplatin for heavily pretreated platinum-resistant ovarian cancer followed by olaparib tablets as maintenance therapy. All three achieved long survival with no evidence of disease (NED).

Case Report

Case 1 (Figure 1). A 48-year-old woman visited our hospital complaining of dysmenorrhea. Transvaginal ultrasonography revealed a multi-cystic right ovarian tumour with a solid compartment. Contrast-enhanced computed tomography (CT) also showed a right ovarian tumour appearing multi-cystic with a solid part, measuring 7×6 cm in size and showing multiple disseminations in the abdominal cavity with ascites. Advanced ovarian cancer was suspected, and surgical management was planned. Initial surgery including abdominal hysterectomy, bilateral adnexectomy and omentectomy was performed. Peritoneal implants present on the surface of the meso-colon and diaphragm were unresectable, and this surgery was deemed suboptimal. Histopathological diagnosis was high-grade serous carcinoma (HGSC) and the patient was staged as having stage IIIC ovarian cancer according to the International Federation of Gynecology and Obstetrics (FIGO) criteria (20). TC therapy [175 mg/m^2 paclitaxel, and carboplatin area under the curve (AUC) 6] was administered for five courses. After that time, no tumour was detectable on CT, so she was considered to have achieved complete clinical response (CR). Sixteen months later, tumours of the liver and pelvic lymph nodes were detected on CT, and recurrence was diagnosed. Five courses of TC therapy were administered again and CR was again seen but progression of pelvic lymph nodes was detected 5 months later, and we judged her disease as platinum-resistant. PLD at 40 mg/m^2 on day 1 with bevacizumab at 15 mg/m^2 day 1 in a 28-day cycle was started, but new pelvic tumours appeared after four courses of this regimen. We thus performed resection of pelvic tumours followed by pelvic radiotherapy. However, only 2 months after radiotherapy, another pelvic tumour was detected; chemotherapy with gemcitabine (1,000 mg/m^2 on days 1, 8 and 15 in a 28-day cycle) was started. A new para-rectal tumour was detected after three courses of gemcitabine. This tumour had invaded the rectal mucosa as diagnosed by colon fiberscopy and the patient complained of symptoms associated with bowel obstruction. Low anterior rectal resection with mechanical anastomosis was performed. Two months postoperatively, multiple new pelvic tumours and a liver tumour were revealed. These tumours caused right hydronephrosis and pelvic pain, therefore analgesics were started. The chemotherapy regimen was thus changed to topotecan (1.25 mg/m^2 on days 1-5), and three courses of this regimen were administered. However, the tumours enlarged, so weekly nedaplatin was started (30 mg/m^2 on days 1, 8 and 15 of a 28-day cycle). Five months after starting weekly nedaplatin, no tumours or hydronephrosis were detected on CT and we considered CR to have been achieved. The patient wanted to stop taking this chemotherapy because of the prolonged consecutive treatments. Surprisingly, she remained NED- and treatment-free for 14 months. However, pelvic and liver tumours were detected on CT again, and weekly nedaplatin was resumed. After three courses of this regimen, CR was achieved again, therefore we planned to start olaparib to maintain this condition. Informed consent was obtained and the patient started taking olaparib tablets (300 mg twice a day). The patient now shows NED, as of 54 months after being classified as platinum-resistant, 30 months after starting weekly nedaplatin and 8 months after starting olaparib. Adverse events during weekly nedaplatin comprised grade 1 nausea that was well controlled by a single dose of metoclopramide. Adverse events during olaparib comprised grade 1 vomiting that was well controlled by metoclopramide and gradually improved over several months.

Case 2 (Figure 2). A 60-year-old woman was referred to our hospital with ovarian tumour, multiple disseminations in the peritoneum, and multiple swellings of the pelvic and para-aortic lymph nodes. She was diagnosed with stage IIIC ovarian carcinoma preoperatively, and initial surgery was planned. Surgical management including abdominal hysterectomy, bilateral adnexectomy, omentectomy, and pelvic and para-aortic lymph adenectomy was performed but some unresectable tumour was seen, and the surgery was considered suboptimal. Histopathological diagnosis was HGSC with multiple lymph node metastases (metastasis in 41 out of 72 (56.9%) resected lymph nodes). TC therapy with bevacizumab (175 mg/m^2 paclitaxel, carboplatin AUC 6 and 15 mg/m^2 bevacizumab) was started and the patient underwent interval debulking surgery after four courses of this chemotherapy. Sampling of some peritoneal foci was performed but no malignant tumours were found on histological analysis. After this operation, another three courses of the same regime were administered. At 5 months after the last chemotherapy, the serum CA125 level appeared markedly elevated and positive accumulation of fluorodeoxyglucose was detected in mediastinal lymph nodes on positron-emission tomography (PET)-CT. We thus considered these findings as indicating recurrence and a platinum-resistant condition, therefore PLD with

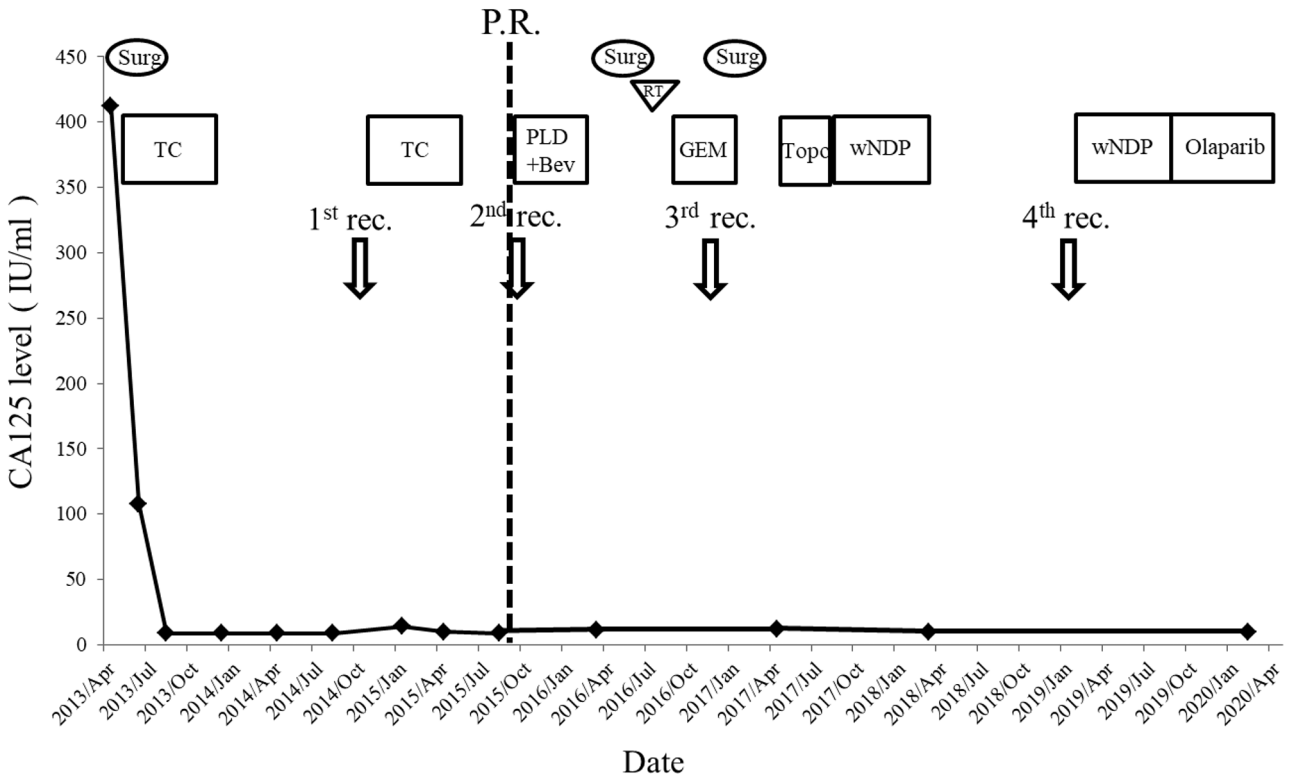

Figure 1. *Clinical flowchart for case 1. CA125: Cancer antigen-125; Surg: surgery; TC: paclitaxel+carboplatin; P.R.: platinum resistant; PLD: pegylated liposomal doxorubicin; Bev: bevacizumab; RT: radiotherapy; GEM: gemcitabine; Topo: topotecan; wNDP; weekly nedaplatin; rec.: recurrence.*

bevacizumab was started. After four courses of this therapy, we checked the brain because of a discrepancy observed between CT and continuously elevated tumour markers. A small solitary metastasis (about 1 cm in diameter) in the cerebellum was revealed. Cyberknife followed by weekly paclitaxel (80 mg/m^2 days 1, 8 and 15 in a 21-day cycle) was performed and brain metastasis was controlled. Eight months after cyberknife therapy, the patient suffered left hemiplegia and visited our hospital. A 3×2-cm tumour in the right front lobe of the brain was detected on CT and magnetic resonance imaging. Resection of the brain metastasis was performed, followed by whole-brain radiotherapy. Her ovarian cancer subsequently remained stable without any therapy for 8 months. At 9 months after the treatment of brain metastasis, re-elevation of CA125 was noted but no disease was apparent on PET-CT. However, the CA125 level remained elevated for 4 consecutive months, therefore we diagnosed tumour marker recurrence. Four courses of weekly nedaplatin were administered and CR of this tumour marker was obtained, with no abnormal findings detected on CT or PET-CT. She was therefore followed-up without therapy. After 6 months, the CA125 level increased again. Weekly nedaplatin was restarted and after four courses of this regimen, partial response (PR) was achieved (21), so we stopped nedaplatin and started olaparib. After starting olaparib, consecutive decreases in CA125 were seen. This patient is now considered to show NED at 46 months after being classified as having platinum-resistant disease, 20 months after starting weekly nedaplatin and 6 months after starting olaparib. No adverse events occurred during weekly nedaplatin and olaparib.

Case 3 (Figure 3). A 74-year-old woman visited another hospital with chief complaint of abdominal distension. She was referred to our hospital because of pelvic ovarian tumour and multiple peritoneal disseminations were detected. Stage IIIC ovarian carcinoma was diagnosed preoperatively, and initial surgery was planned. Surgical management including abdominal hysterectomy, bilateral adnexectomy and omentectomy was performed but some tumours were unresectable and the surgery was thus considered suboptimal. Histopathological diagnosis was HGSC and the patient was classified as having stage IIIC disuse according to FIGO criteria. Therapy of TC with

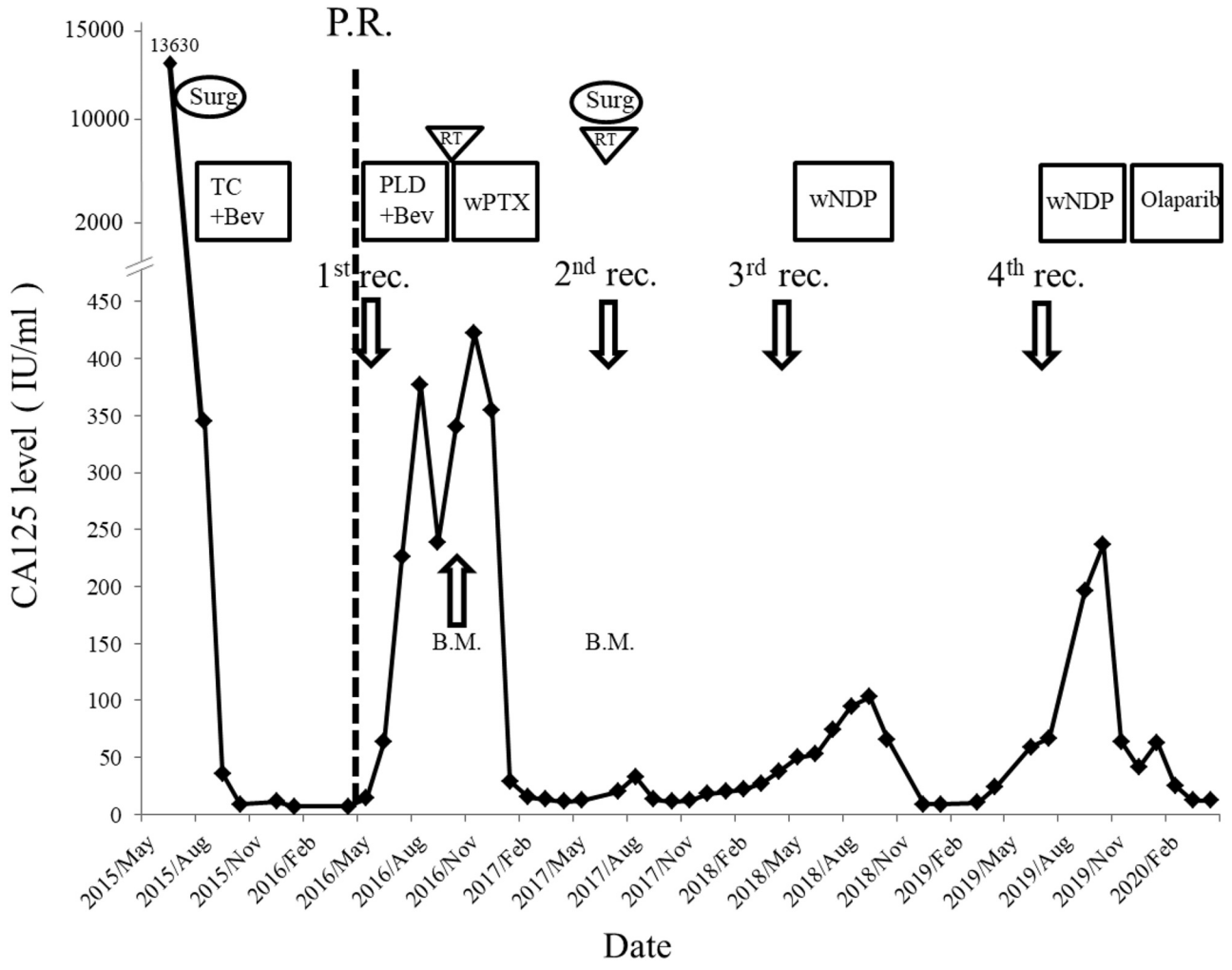

Figure 2. *Clinical flowchart for case 2. CA125: Cancer antigen-125; Surg: surgery; TC: paclitaxel+carboplatin; Bev: bevacizumab; P.R.: platinum resistant; PLD: pegylated liposomal doxorubicin; RT: radiotherapy; B.M.: brain metastasis; wPTX; weekly paclitaxel; wNDP; weekly nedaplatin; rec.: recurrence.*

bevacizumab (175 mg/m^2 paclitaxel, carboplatin AUC 6 and 15 mg/m^2 bevacizumab) was started. After four courses of chemotherapy, she underwent interval debulking surgery. Sampling of some peritoneal foci was performed, and only small amounts of viable tumour were detected, but chemotherapy was considered very effective from histological analysis. After this operation, another three courses of the same regimen were administered and the patient achieved CR. Ten months after the last chemotherapy, the CA125 level was elevated markedly and FDG accumulation was detected in the abdominal cavity on PET-CT. Therapy of TC with bevacizumab was thus resumed. After four courses, CR was shown and chemotherapy was stopped. However, 7 months later, re-elevation of CA125 was detected and new tumours in the liver and in the pelvic cavity were revealed, therefore TC with bevacizumab was started again. After just five courses, progressive disease was shown, and the tumour was considered platinum-resistant. PLD with bevacizumab was started and stable disease was maintained for several months, but after just seven courses of this therapy, new liver tumour was detected along with markedly elevated CA125 level. Weekly nedaplatin was therefore started. PR was achieved after three courses of this regimen, and olaparib was started. This patient now shows NED, 29 months after being classified as having platinum-resistant disease, 17 months from starting weekly nedaplatin, and 13 months after starting olaparib. Adverse events did not occur during weekly nedaplatin administration, whereas during olaparib, grade 4 anaemia occurred, which warranted blood transfusion. After dose reduction, olaparib was continued safely.

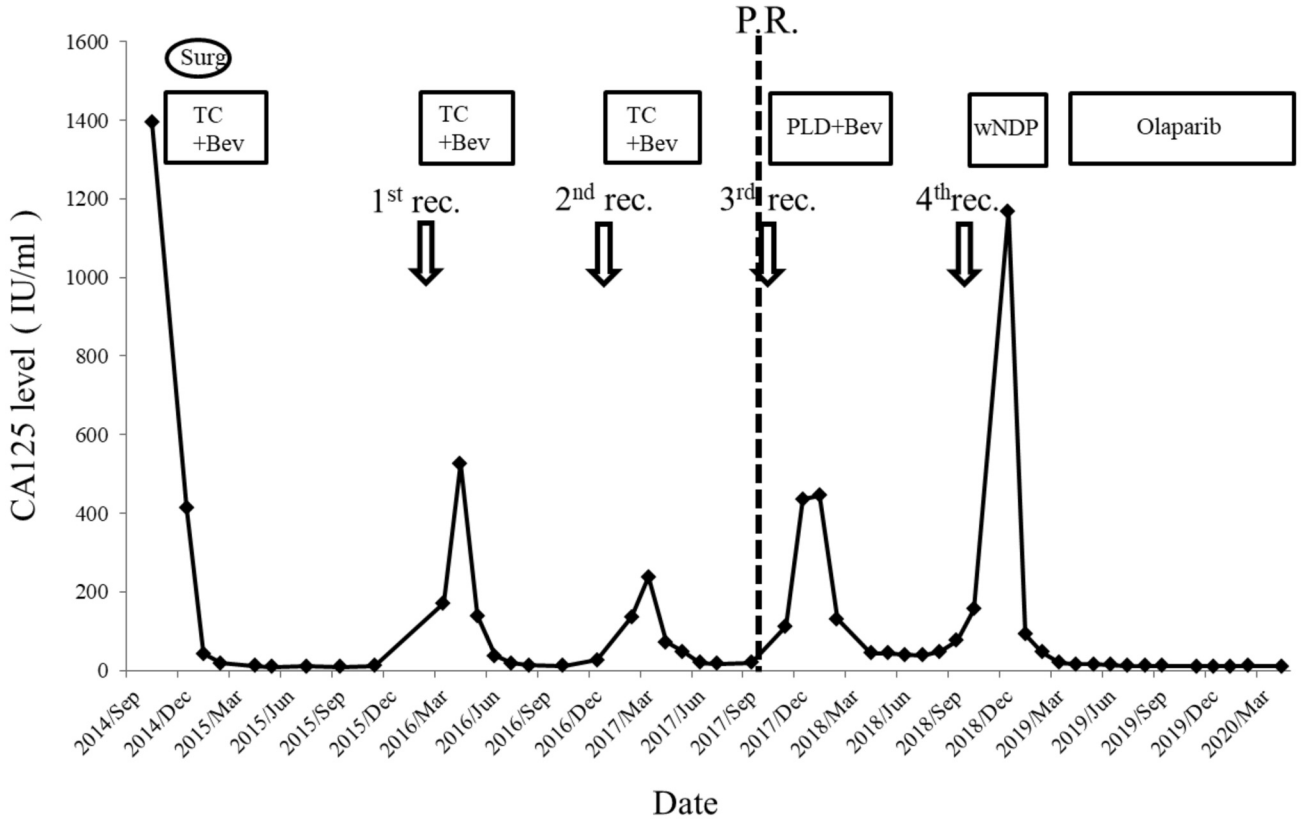

Figure 3. *Clinical flowchart for case 3. CA125: Cancer antigen-125; Surg: surgery; TC: paclitaxel+carboplatin; Bev: bevacizumab; P.R.: platinum resistant; PLD: pegylated liposomal doxorubicin; RT: radiotherapy; wNDP; weekly nedaplatin; rec.: recurrence; CA125: cancer antigen-125.*

Discussion

In this case report, two fascinating results were identified. Firstly, out of three patients treated with weekly nedaplatin who had been treated with platinum-combination regimens and non-platinum single-agent regimens because of platinum resistance, two achieved CR for and one PR. All cases clearly demonstrated that weekly nedaplatin contributed to the prolongation of patient survival (Figures 1-3). Secondly, olaparib tablets were safely administered as maintenance therapy following weekly nedaplatin for the treatment of platinum-resistant ovarian carcinoma, and all three patients have shown NED for 6-12 months.

In terms of the impact of weekly nedaplatin, case 1 received four non-platinum agents, case 2 received two non-platinum agents with radiation therapy for brain metastasis and case 3 received one non-platinum regime but the timing of nedaplatin administration followed diagnosis of a new liver tumour with aggressive elevation of CA125, so all three patients were considered to be in quite a severe condition. Leitato *et al*. reported that platinum re-treatment using carboplatin or cisplatin showed objective response in seven out of 30 (23%) patients with platinum-resistant disease (PR, 23%; CR, 0%) (16). In addition, they described patients without objective response to the prior platinum therapy or more than three intervening treatments as being unlikely to respond to subsequent platinum therapy (16). Considering such results, our results for case 1 were both surprising and excellent but the timing of platinum retreatment must be considered. Goto *et al*. reported that nedaplatin for the treatment of platinum-/taxane-resistant ovarian cancer led to a response of 24% (4/17) (2 CRs, 2 PRs), and the present study is only the second to discuss platinum retreatment using nedaplatin (18). Important differences exist between the report by Goto *et al*. and our own. The dose of nedaplatin used by Goto *et al*. was 90 mg/m^2 on day 1 of a 28-day cycle, whereas ours was 30 mg/m^2 on days 1, 8 and 15 of a 28-day cycle (18). Nedaplatin is a second-generation platinum analogue that is significantly less nephrotoxic than both cisplatin and carboplatin (22-24). Preclinical and clinical studies have demonstrated that nedaplatin exerts anticancer activity superior to that of carboplatin and equivalent to that of cisplatin (24). For the treatment of ovarian cancer, comparable survival time and similar toxicity

of nedaplatin were reported in patients treated with this agent either as initial treatment or for platinum-sensitive recurrence (25-27). Our Department has used weekly nedaplatin for ovarian cancer with the expectation that the rate of adverse events may be lower compared to monthly nedaplatin, although this is just the experience of our Department and has not been evaluated scientifically. Exact evaluation of the efficacy of platinum retreatment according to the type of platinum agent used has not been elucidated. Moreover, doses and schedules have also not been evaluated in detail. In the future, these questions should be investigated in a clinical trial.

The second feature of these cases was the application of olaparib tablets as maintenance for patients with platinum-resistant disease who successfully received platinum retreatment with weekly nedaplatin. Olaparib is a poly (ADP-ribose) polymerase inhibitor that targets tumours showing homologous recombination repair defects, such as mutations of breast-related cancer antigen (*BRCA*) by a process known as synthetic lethality (5). Olaparib was approved by the US Food and Drug Administration for the treatment of platinum-sensitive recurrent ovarian cancer regardless of *BRCA* mutation status in 2017, based on Study 19 and SOLO2 (5, 28-30). The advent of olaparib has had a great impact on ovarian cancer treatment, allowing some patients with advanced cancer to achieve long survival. Almost 25% of patients in Study 19 received olaparib for 2 or more years and over 10% continued treatment for 6 years or more, demonstrating a prolonged, clinically meaningful benefit from olaparib maintenance therapy, unprecedented in patients with recurrent ovarian cancer (31, 32). Moreover, olaparib was approved as a front-line maintenance therapy for patients with *BRCA* mutation based on SOLO1 (33). Recently, olaparib was reported to achieve significant and clinically relevant improvements in overall response rate and PFS compared with non-platinum chemotherapy in patients with germline *BRCA*-mutated platinum-resistant relapsed ovarian cancer by SOLO3 (34). Olaparib will thus be adapted to many situations of ovarian cancer treatment according to *BRCA* mutation in the future. When we recognised the good results achieved with weekly nedaplatin in our three patients, we considered that despite these positive responses, continued use of the regimen would eventually lead to the patients resuming a platinum-resistant status. We thus recommended olaparib for maintenance therapy in these patients in the hope of retaining a stable disease state for as long as possible. This is challenging because little evidence has been accumulated for patients in this setting and no definition has been established for successful platinum retreatment in order to define a platinum-sensitive state supporting the use of olaparib. Interestingly, some reports have described homologous recombination deficiency as being correlated with not only long-term response to olaparib (30, 31), but also with the efficacy of platinum retreatment (19).

This study is only a report of three cases, and therefore we cannot reach any definitive conclusions, but encouraging long-term survival was achieved with weekly nedaplatin as platinum retreatment followed by olaparib for platinum-resistant patients, and further prospective study is warranted.

Conflicts of Interest

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. Furthermore, none of the Authors have any commercial or financial involvement in connection with this study that represent or appear to represent any conflicts of interest.

Authors' Contributions

Study conception: SS, SF and KF. Patient management: All Authors. Data acquisition: SS and NK. Article drafting: SS. Article revision: SS and TT.

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