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Efficacy of cisplatin combined with topotecan in patients with advanced or recurrent ovarian cancer as second- or higher-line palliative chemotherapy

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Abstract

The aim of this study was to evaluate the outcomes of patients with advanced or recurrent ovarian cancer treated with cisplatin combined with topotecan as second- or higher-line palliative chemotherapy.

We retrospectively reviewed the medical records of patients with advanced or recurrent ovarian cancer, who were treated with cisplatin (50 mg/m^2 on day 1) and topotecan (0.75 mg/m^2 on days 1–3). Treatment response, progression-free survival (PFS) and overall survival (OS) were analyzed, and laboratory data were reviewed to evaluate toxicities.

Thirty one patients were treated with cisplatin and topotecan. The objective response rate (ORR) was 22.6%, and the disease control rate (DCR) was 61.3%. The median PFS was 3.7 months (95% confidence interval [CI], 2.3–5.2 months) and the median OS was 44.5 months (95% CI, 35.5–53.5 months). The ORR (33.3% vs. 0%; $P = .012$) was significantly better in the platinum-sensitive group compared to the platinum-resistant group. The median PFS was significantly longer in the platinum-sensitive group compared to the platinum-resistant group (7.7 vs 2.5 months; $P < .001$), and the median OS was also significantly longer in the platinum-sensitive group (46.6 vs 19.3 months; $P < .001$). Almost all of the patients reported some degree of hematological toxicity. A high rate of grade 3–4 neutropenia (87.1%) was observed. Grade 3–4 thrombocytopenia (41.9%) and febrile neutropenia (19.4%) were also seen.

The results showed that cisplatin combined with topotecan, as second- or higher-line palliative chemotherapy for patients with advanced or recurrent ovarian cancer, might be effective, especially in the platinum-sensitive group. However, attention should be paid to the high hematological toxicity associated with this drug combination.

Abbreviations: ANC = absolute neutrophil count, CI = confidence interval, CR = complete response, DCR = disease control rate, DNA = deoxyribonucleic acid, G-CSF = granulocyte colony stimulating factor, ORR = overall response rate, OS = overall survival, PARP = poly ADP-ribose polymerase, PD = progressive disease, PFS = progression-free survival, PR = partial response, RECIST = response evaluation criteria in solid tumor, SD = stable disease, UNL = upper limit of normal, VEFG = vascular endothelial growth factor.

Keywords: cisplatin, ovarian cancer, palliative chemotherapy, topotecan

1. Introduction

Ovarian cancer is the third most common, and second most lethal, gynecological malignancy in the world.[1] Because ovarian cancer usually lacks distinct symptoms, and there are no effective screening tools in the early stage, more than 70% of patients are diagnosed with the disease in advanced stages. Thus, most ovarian cancers are incurable, and treatments focus on palliation of disease to slow its progress, increase the patients lifespan and improve quality of life. Due to gradual improvements in

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treatments and the development of new drugs, ovarian cancer can now be managed like a chronic disease.[2,3]

In advanced ovarian cancer, the standard treatment is maximal debulking surgery to remove all visible lesions, followed by chemotherapy.[4,5] For almost 40 years, first-line chemotherapy regimens have usually been based on platinum doublet chemotherapy. A previous study demonstrated a significant increase in survival when paclitaxel was used in combination with platinum,[6] and platinum/taxane doublet is now firmly established as the first-line chemotherapy regimen.[7]

The water-soluble camptothecin analog topotecan is a cytotoxic agent that inhibits topoisomerase I and cleaves double-stranded deoxyribonucleic acid (DNA) during replication in the S phase, leading to cell death.[8] Several prior studies have revealed that topotecan has efficacy in the treatment of recurrent ovarian cancer.[9–13] Topotecan monotherapy has proven usefulness in patients with ovarian cancer, especially in platinum resistant group. For this reason, topotecan monotherapy is recommended in NCCN guidelines as one of the treatment option in platinum resistant ovarian cancer.[14] Cisplatin is platinum-based drug as carboplatin, which is used for the treatment of ovarian cancer, particularly cisplatin alone or in combination with gemcitabine as a treatment option for platinum sensitive ovarian cancer.[14] However, there are few data on the efficacy of cisplatin and topotecan combination regimen in ovarian cancer patients. In a first-line setting, Hoskins et al[15] reported the outcomes of cisplatin and topotecan combination therapy in advanced ovarian cancer, in a phase III randomized study comparing sequential cisplatin-topotecan and carboplatin-paclitaxel with carboplatin-paclitaxel. The results showed similar efficacy between the 2 groups, although toxicity was more severe in the cisplatin-topotecan group. Likewise, few data exist regarding the use of cisplatin combined with topotecan as second- or higher-line palliative chemotherapy in patients with advanced or recurrent ovarian cancer, even though this regimen could be an option for the treatment of advanced or recurrent ovarian cancer.[15–17] Against this background, we evaluated the clinical outcomes of advanced ovarian cancer patients treated with cisplatin combined with topotecan as second- or higher-line palliative therapy.

2. Methods

2.1. Patients

We collected and reviewed the medical records of patients diagnosed with advanced or relapsed ovarian cancer, and who were treated with cisplatin plus topotecan as a second- or higher-line palliative chemotherapy from March 2009 to June 2019 at Chungnam National University Hospital, Daejeon, Republic of Korea. We included patients ≥18 years of age with histologically or cytologically confirmed advanced or relapsed ovarian cancer. Other inclusion criteria included the presence of at least 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumor (RECIST, version 1.1) criteria, an Eastern Cooperative Oncology Group performance score ≤ 2, previous treatment with at least 1 palliative systemic chemotherapy regimen, an absolute neutrophil count (ANC) ≥ 1500/ml and platelet count ≥100,000/ml, a serum creatinine level ≤1.5-fold the institutional upper limit of normal (ULN), a serum bilirubin level ≤1.5-fold the ULN, and an alkaline phosphatase level ≤2.5-fold the ULN. We excluded patients who had other malignancies within the last 5 years, patients who had previously received non-cytotoxic therapies (e.g., vascular endothelial growth factor [VEGF] or poly ADP-ribose polymerase [PARP] inhibitor monotherapy), patients who had not received cytoreductive surgery, patients requiring hospital admission for active bleeding and central nervous system disease, and patients who have active infection requiring systemic therapy at the initiation of the study treatment. Other exclusion criteria included significant cardiovascular disease (e.g., uncontrolled hypertension, unstable angina, uncontrolled congestive heart failure, or uncontrolled arrhythmias), pregnancy or nursing, or a major surgical procedure within the last 30 days. This study was approved by the Institutional Review Board of Chungnam National University Hospital.

2.2. Treatment

The patients were treated with cisplatin (50 mg/m^2 for 1 day) and topotecan (0.75 mg/m^2 for 3 days) and the cycles were repeated every 21 days. The cycles were delayed if the ANC was < 1500/ml, and/or the platelet count was <100,000/ml on the proposed day of treatment. All patients received prophylactic medication for chemotherapy-induced nausea/vomiting. Granulocyte colony-stimulating factor (G-CSF) was administered to patients with ANC < 500/ml or febrile neutropenia. Chemotherapy was continued until disease progression, unacceptable toxicity, or patient refusal (maximum of 6 cycles).

2.3. Response and toxicity assessment

Response evaluations were performed according to clinical assessments and imaging studies, after every 2 or 3 cycles, in the absence of overt progression. The treatment response was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the RECIST criteria (version 1.1), and toxicity was evaluated based on the NCI Common Toxicity Criteria (CTC; version 5.0).

2.4. Statistical analysis

Basic descriptive statistics were obtained, including medians with ranges. Differences between groups were tested using the Chi-Squared test for categorical variables. Progression-free survival (PFS) was defined as the time between the first administration of chemotherapy and the date of tumor progression. Overall survival (OS) was defined as the time between the first administration of chemotherapy and the date of last contact or death. PFS and OS were estimated using the Kaplan–Meier method with the log-rank test. A P value <.05 was considered significant. SPSS statistical software for Windows (version 25.0; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

3. Results

3.1. Patient population

Thirty one patients with advanced or relapsed ovarian cancer were treated with cisplatin combined with topotecan as a second- or higher-line palliative chemotherapy. The median patient age was 59 years (range: 44–78 years). The histological subtypes were as follows:

- serous carcinoma (n = 20),
- transitional cell carcinoma (n = 2),

Table 1

Baseline characteristics.

Characteristics	No. (%)
Total number	31
Age (y; median, range)	59 (44–78)
Histological type	
Serous carcinoma	20 (64.5)
Transitional cell carcinoma	2 (6.5)
Mucinous carcinoma	2 (6.5)
Clear cell carcinoma	2 (6.5)
Others	5 (16.1)
Platinum sensitivity	
Platinum-sensitive	21 (67.7)
Platinum-resistant	10 (32.3)
No. prior regimens	
1	9 (29.0)
2	12 (38.7)
3	8 (25.8)
≥4	2 (6.5)

- mucinous carcinoma (n=2),
- clear cell carcinoma (n=2), and others (n=5).

All of the patients had undergone platinum-based cytotoxic chemotherapy before the study treatment. Platinum sensitivity was measured from the time of completion of platinum-based adjuvant chemotherapy to disease progression, and the intersection was 6 months. Ten patients (32.3%) were in the platinum-resistance group, and 21 were (67.7%) in the platinum-sensitive group (Table 1).

3.2. Tumor responses

CR was observed in no cases, while a PR was observed in 7 (22.6%) patients. SD was observed in 12 (38.7%) patients, and PD was observed in 12 (38.7%) patients. The objective response rate (ORR) was 22.6% and the disease control rate (DCR) was 61.3% (Table 2). The ORR (33.3% vs 0%; $P=.012$) was significantly better in the platinum-sensitive group compared to the platinum-resistant group (Table 3). The tumor response according to number of prior regimens was not significantly different, although the ORR (33.3% vs 18.2%; $P=.439$) tended to be higher in the patients treated with 1 prior regimen (Supplementary Table 1, http://links.lww.com/MD/E112). Fifteen patients had been retreated with paclitaxel and carboplatin after recurrence or progression following initial cytoreductive surgery and adjuvant chemotherapy. Among them, 12 (80.0%) patients showed at least PR to first-line paclitaxel/carboplatin (responder), and 3 (20.0%) patients did not show any tumor response (non-responder). The ORR was higher in the responder group compared with the non-responder group (41.7% vs 0%; $P=.016$), and the DCR was also better in the responder group (83.3% vs 0%; $P=.004$) (Supplementary Table 2, http://links.lww.com/MD/E112).

Table 2

Best response to combination of cisplatin and topotecan (n=31).

Response	No. (%)
CR	0 (0)
PR	7 (22.6)
SD	12 (38.7)
PD	12 (38.7)
ORR	7 (22.6)
DCR	19 (61.3)

CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease, ORR = objective response rate, DCR = disease control rate.

Table 3

Best response to combination of cisplatin and topotecan according to platinum sensitivity (n=31).

Response	Platinum-resistant No. (%)	Platinum-sensitive No. (%)	*P*-value
CR	0 (0)	0 (0)	.029
PR	0 (0)	7 (33.3)	
SD	4 (40.0)	8 (38.1)	
PD	6 (60.0)	6 (28.6)	
ORR	0 (0)	7 (33.3)	.012
DCR	4 (40.0)	15 (71.4)	.095

CR = complete response, PD = progressive disease, PR = partial response; SD = stable disease, ORR = objective response rate, DCR = disease control rate.

3.3. Survival outcomes

In all patients, the median PFS was 3.7 months (95% confidence interval [CI], 2.3–5.2) (Fig. 1) and the median OS was 44.5 months (95% CI, 35.5–53.3) (Fig. 2). The median PFS was significantly longer in the platinum-sensitive group compared to the platinum-resistant group (7.7 vs 2.5 months; $P<.001$) (Fig. 3), and the median OS was also significantly longer in the platinum-sensitive group (46.6 vs 19.3 months; $P<.001$) (Fig. 4). The median PFS was longer in the responder group compared with the non-responder group (7.7 vs 2.5 months; $P<.001$) (Supplementary Fig. 1, http://links.lww.com/MD/E112), and the median OS was also longer in the responder group (46.6 vs 19.3 months; $P<.001$) (Supplementary Fig. 2, http://links.lww.com/MD/E112).

3.4. Safety profiles

A total of 132 cycles of cisplatin and topotecan combination treatment were administered (median, 4.3 cycles/patient; range: 1–6 cycles/patient). Almost all of the patients reported some degree of hematological toxicity at least once. The rate of neutropenia was 100% for any grade, and 87.1% for grade 3–4. The rate of thrombocytopenia was 67.7% for any grade and 41.9% for grade 3–4. The rate of anemia was a 96.8% for any grade and 77.4% for grades 3–4. Febrile neutropenia developed in 6 (19.4%) patients, and no patients died due to febrile neutropenia. For any grades, non-hematological toxicities included increased levels of creatinine in 3.2% of cases, alanine aminotransferase in 25.8% and bilirubin in 12.9%. No non-hematological toxicities were seen in those of grade 3–4 (Table 4).

4. Discussion

The initial treatment for advanced ovarian cancer is well established, i.e., cytoreductive surgery followed by platinum plus taxane combination chemotherapy. The aim of surgery is to achieve complete resection of macroscopic residuals, where complete resection of all macroscopic disease has been shown to be the single most important independent prognostic factor in advanced ovarian cancer.[18] After surgery, patients are treated with platinum and taxane combination regimes for 6 cycles.

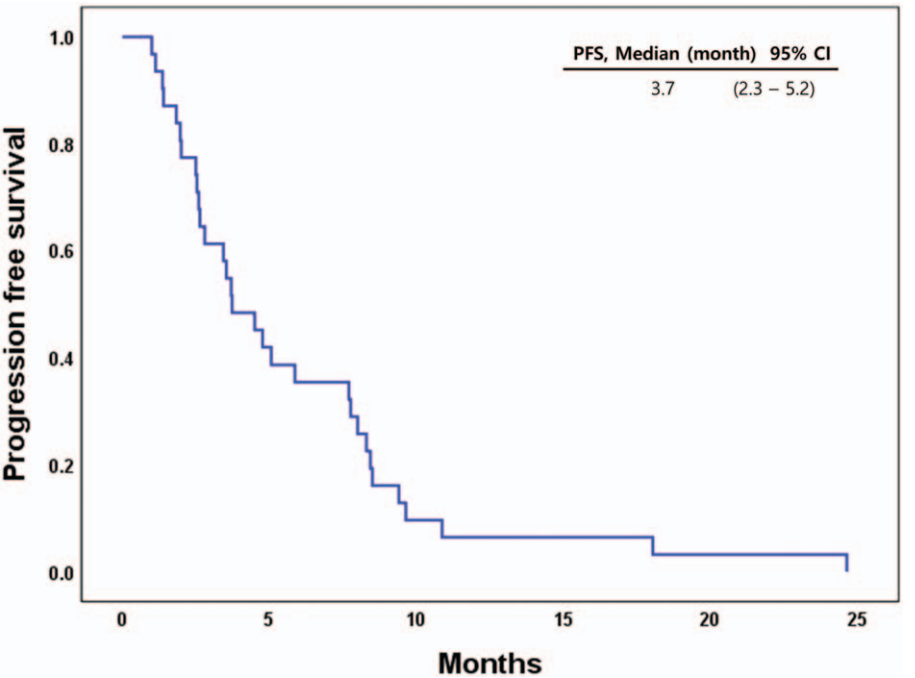

Figure 1. Progression-free survival for all patients (n=31).

However, even with successful front-line treatment, most patients relapse and about 50% to 80% ultimately require salvage therapy.[16] Therefore, additional palliative chemotherapy is inevitable, and in these cases the palliative chemotherapy regimen is determined by platinum sensitivity.[19]

Platinum sensitivity is one of the most important factors in palliative chemotherapy. Platinum-resistant disease is defined as progression within 6 months of the last platinum-containing regimen, while platinum-sensitive disease has been defined as progression after 6 months. Patients showing recurrence within 6 to 12 months may be reclassified as partially sensitive, and those experiencing relapse after 12 months as highly sensitive.[20,21] In platinum-sensitive patients, a combination treatment such as cisplatin or carboplatin with paclitaxel, gemcitabine, or

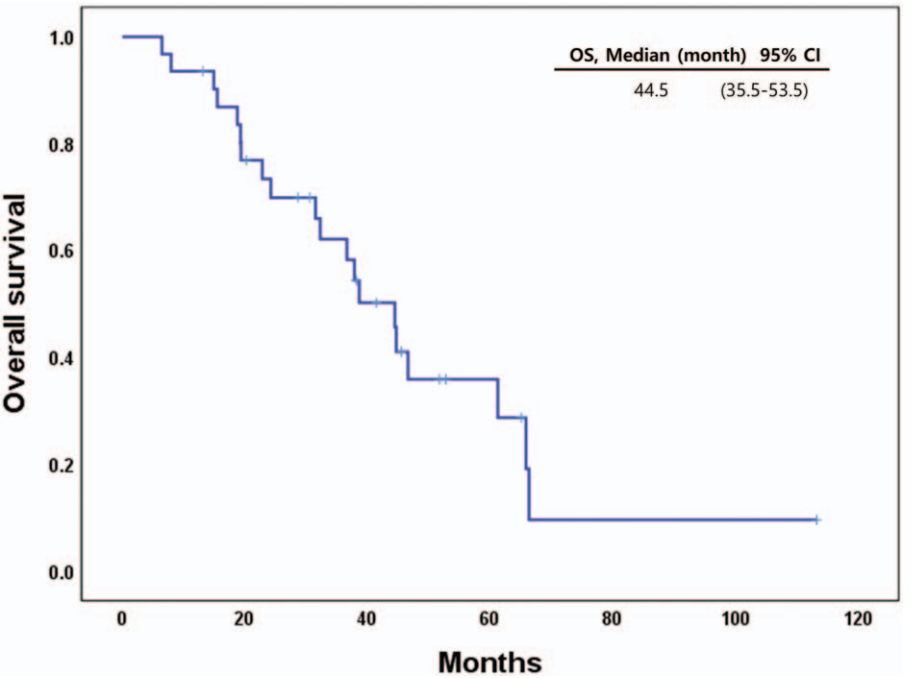

Figure 2. Overall survival for all patients (n=31).

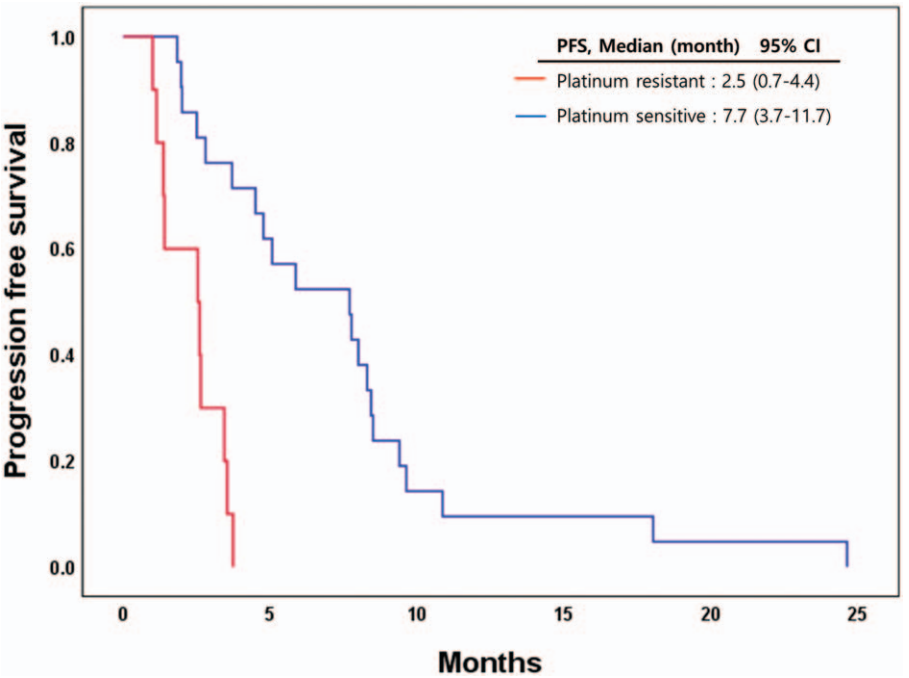

Figure 3. Progression-free survival between platinum-sensitive (n=21) and platinum-resistant (n=10) groups.

pegylated liposomal doxorubicin is generally used. Most of these drugs are associated with a PFS of 12 to 15 months.[7,19] On the other hand, platinum-resistant patients have a poor PFS. In these cases, the standard treatment is not well established but mainly monotherapies, such as pegylated liposomal doxorubicin and topotecan, are used.[7]

Recent therapeutic approaches include the addition of bevacizumab to conventional chemo-regimens and weekly dose-dense paclitaxel therapy; these have been shown to increase OS and are increasingly being used as first-line palliative chemotherapies instead of the existing standard therapies.[22–25] In addition, PARP inhibitors, such as olaparib, are being used in palliative therapy for recurrent ovarian cancer.[26] Although there are many options to choose from, ovarian cancer patients have a relatively long life, so treating them with new drug combinations is still important.[19]

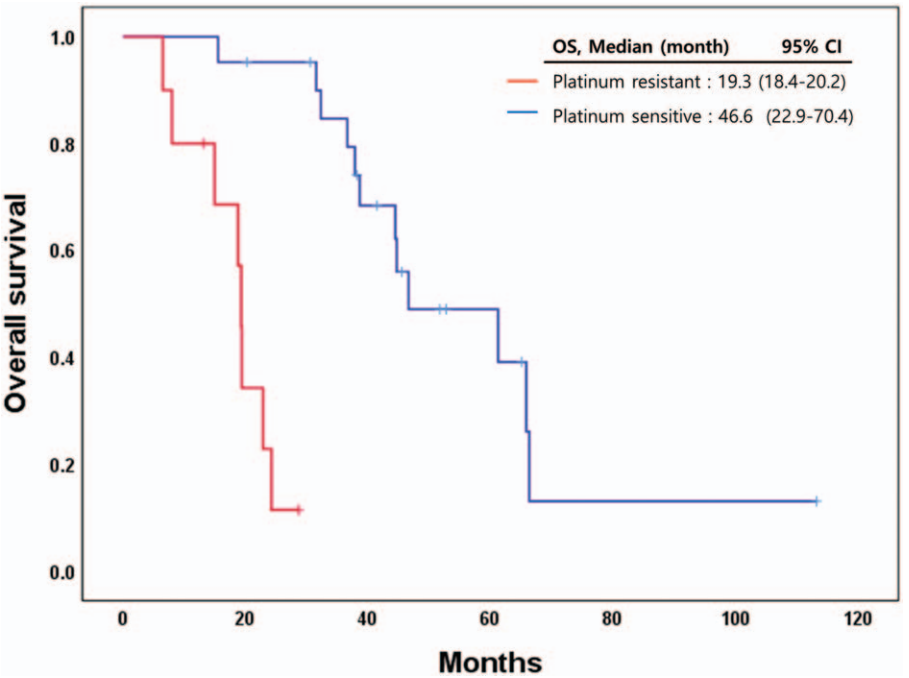

Figure 4. Overall survival between platinum-sensitive (n=21) and platinum resistant (n=10) groups.

Table 4

Laboratory toxicities (n = 31).

Toxicity	Any grade No. (%)	Grade 3 or 4 No. (%)
Hematologic		
Anemia	30 (96.8)	24 (77.4)
Thrombocytopenia	21 (67.7)	13 (41.9)
Neutropenia	31 (100)	27 (87.1)
Febrile neutropenia	-	6 (19.4)
Non-hematologic		
ALT elevation	8 (25.8)	0 (0)
TB elevation	4 (12.9)	0 (0)
Cr elevation	1 (3.2)	0 (0)

ALT = alanine aminotransferase, TB = total bilirubin; Cr = creatinine.

As mentioned earlier, a prior study showed non-inferiority of a combination of cisplatin and topotecan as a first-line therapy in advanced ovarian cancer compared to carboplatin-paclitaxel.[15] The patients in that phase III study were administered cisplatin 50 mg/m^2 on day 1 and topotecan 0.75 mg/m^2 for 5 consecutive days. The patients in the study group had substantially higher myelotoxicity than those in the control group; specifically, 85% had grade 4 granulocytopenia and 22% had febrile neutropenia or infection with grade 3–4 neutropenia.[15] Another study reported the effect of cisplatin combined with topotecan as third- or higher-line palliative chemotherapy.[16] In that study, 1.0 mg/m^2 of topotecan was administered for 5 consecutive days and 50 mg/m^2 of cisplatin on day 1. The dose of topotecan was reduced by 0.25 mg/m^2/day if grade 3–4 toxicity developed within 14 days. The study showed an ORR of 30%, but 90% of the patients had grade 3–4 neutropenia and 65% had thrombocytopenia.[16] Another small phase II study (n = 15) used 0.6 mg/m^2/day of topotecan for 5 days and 50 mg/m^2 of cisplatin on day 1, as third- or higher-line chemotherapy for the treatment of recurrent ovarian cancer.[17] In this study, the ORR was 13.3% and grade 4 thrombocytopenia and neutropenia occurred in 30% and 45% of patients, respectively. Although this study reported a relatively tolerable toxicity profile, the response rate was relatively low compared to other studies.[17] Thus it is important to reduce toxicity while maintaining efficacy. One way to ameliorate hematologic toxicity is to use a different administration schedule.[27,28] In support of this strategy, in studies on uterine cervical cancer patients, 50 mg/m^2 cisplatin for 1 day and 0.75 mg/m^2 topotecan for 3 days was used as the standard dose.[8,29] In these studies, 49.1% to 70% of the patients had grade 3–4 neutropenia and 16.3% to 31.3% had grade 3–4 thrombocytopenia; however, in almost all cases, the cytopenia was tolerable and manageable.[8,29] Although these results were obtained in the context of cervical cancer and not ovarian cancer, the relatively tolerable toxicity prompted speculation that this regimen could be used in ovarian cancer.

In this retrospective, single-center study, the combination of cisplatin and topotecan, as second- or higher-line palliative chemotherapy, showed clinical efficacy in women with recurrent ovarian cancer. The ORR was 22.6% and the DCR was 61.3%, similar to other second-line chemotherapy regimens.[30–32] The median PFS and OS were 3.7 and 44.5 months, respectively, thus also indicating similar efficacy to other second-line chemotherapy regimens.[30–32] The effect was more significant in the platinum-sensitive group than the platinum-resistant group, with an ORR of 33.3% and 0% and median PFS of 7.7 and 2.5 months, respectively. However, hematologic toxicity occurred in almost all of the patients. Specifically, 87.1% had grade 3 or higher neutropenia, 41.9% had grade 3 or higher thrombocytopenia, and 19.4% had febrile neutropenia. Fortunately, the cases showing toxicity were well managed via G-CSF administration, antibiotics and best supportive care, although it is strongly suggested that the condition of the patient should be considered very carefully before drug administration.

This study had several limitations. First, the number of patients assessed was low, at 31, which limited the statistical power. Second, as a result of the retrospective design, several types of bias affected the results pertaining to the effects and side effects of the combination regimen. Third, this study was a single-center study, so the patient population was relatively homogeneous. Finally, data on patient-reported outcomes, such as quality of life, were not available. Hence a well-designed and controlled prospective study is needed.

In conclusion, although the small number of patients and retrospective nature of this study represent major limitations, the use of cisplatin combined with topotecan, as second or higher-line palliative chemotherapy for advanced or recurrent ovarian cancer patients, might be effective, especially in platinum-sensitive patients. However, clinicians should manage the patient carefully due to the high hematological toxicity of this regimen.

Author contributions

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