A Phase II Nonrandomized Study of Oxaliplatin/Doxorubicin Combination Therapy in the Treatment of Recurrent Ovarian Cancer

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Abstract
The study was aimed at evaluating oxaliplatin/doxorubicin combination therapy in recurrent ovarian cancer. Patients with recurrent ovarian cancer in whom the platinum-free interval had been < 24 months received doxorubicin/oxaliplatin. The median progression-free survival times in platinum-sensitive and platinum-resistant cancer were 10.8 and 6.7 months, respectively. The combination of oxaliplatin/doxorubicin is an active regimen in both platinum-sensitive and platinum-resistant ovarian cancer.

Introduction: This study was aimed at evaluating the efficacy and tolerability of oxaliplatin/doxorubicin combination therapy in patients with platinum-sensitive and platinum-resistant ovarian cancer. Materials and Methods: Patients with recurrent ovarian cancer after 1 regimen of platinum-based chemotherapy received doxorubicin (50 mg/m² intravenously) and oxaliplatin (130 mg/m² intravenously) on day 1 every 3 weeks. The platinum-free interval was set to be < 24 months. Results: A total of 33 patients were enrolled (21 platinum-resistant and 12 platinum-sensitive relapses). The response rate in platinum-resistant ovarian cancer was lower than in platinum-sensitive disease (33.4% vs. 54.5%), although the difference was not statistically significant (P = .59). The median progression-free survival (PFS) and overall survival in the whole cohort were 7.4 and 24.3 months, respectively. PFS in platinum-sensitive cancer was longer than in platinum-resistant cancer (10.8 vs. 6.7 months); however, this difference did not reach statistical significance (P = .14). Conclusion: The combination of oxaliplatin/doxorubicin is an active regimen for patients with platinum-sensitive and platinum-resistant recurrent ovarian cancer.

Introduction
Ovarian cancer is the leading cause of death among women with gynecologic cancer in the world. The high mortality rate is related to the late diagnosis of this disease: more than 70% of ovarian cancers are diagnosed in stage III or IV. Standard treatment, including maximum-effort cytoreductive surgery and platinum-based chemotherapy, results in complete remission in most patients. Unfortunately, almost all patients with advanced ovarian cancer develop recurrent disease despite effective treatment. Current treatment of platinum-sensitive relapses includes a platinum compound (cisplatin or carboplatin) combined with paclitaxel, gemcitabine, pegylated liposomal doxorubicin, or another agent. Treatment of platinum-resistant relapses usually includes monotherapy with any of the potentially active nonplatinum drugs, for example, pegylated liposomal doxorubicin, topotecan, weekly paclitaxel, gemcitabine, or oral etoposide.1 Oxaliplatin is currently an uncommon drug in the treatment of recurrent ovarian cancer. The promising advantage of oxaliplatin is no complete cross-resistance between this drug and other platinum agents in solid tumors.2 Therefore, oxaliplatin showed promising efficacy in both platinum-sensitive and platinum-resistant ovarian cancer in several phase II clinical trials.3-6 The objective response rate for different oxaliplatin-based regimens, including combinations with pegylated liposomal doxorubicin, ranges from 29% to 67%.9-21 Availability of pegylated liposomal doxorubicin is limited owing to its high cost. On the other hand, the efficacy of conventional doxorubicin is not
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inferior to that of pegylated liposomal doxorubicin. The only randomized study that compared the efficacy of the 2 drugs was conducted in metastatic breast cancer. It showed similar efficacy of conventional doxorubicin and pegylated liposomal doxorubicin but different safety profiles.22

Therefore, the aim of the present phase II nonrandomized study was to determine the efficacy and tolerability of oxaliplatin/doxorubicin combination therapy in patients with recurrent ovarian cancer. This study focused mostly on patients with platinum-resistant cancer, relying on the concept of no complete cross-resistance between oxaliplatin and carboplatin. However, the study also included patients with platinum-sensitive cancer who had had a platinum-free interval (PFI) of < 24 months. It was supposed that these patients could benefit from the change of a platinum compound to overcome potential resistance. Patients with very platinum-sensitive ovarian cancer (PFI > 24 months) were excluded, because generally these patients get maximum advantage from reintroduction of a previous platinum-based regimen.23

Materials and Methods

Study Design

This is a single-institution prospective nonrandomized phase II study evaluating oxaliplatin/doxorubicin combination therapy in patients with platinum-sensitive or platinum-resistant ovarian cancer. The study protocol and the related consent form were approved by the Ethics Committee of the authors’ institution. All patients enrolled in the study received doxorubicin 50mg/m² intravenously over 15 minutes followed by oxaliplatin 130 mg/m² intravenously over 120 minutes on day 1 every 3 weeks. All patients were expected to receive 6 cycles followed by surveillance every 8 weeks until disease progression.

The next cycle of chemotherapy was not administered unless the absolute neutrophil count was > 1500 cells/µL and the platelet count was > 100,000 cells/µL. Support with granulocyte colony-stimulating factors or erythropoiesis-stimulating agents was allowed according to the American Society of Clinical Oncology guidelines.26,27 In case of treatment-related adverse events leading to a cycle delay of > 4 days, dose reductions of both drugs were allowed.

Assessment of Response and Evaluation of Toxicity

To evaluate the disease sites, all patients underwent abdominal ultrasonography or computed tomography scan and serum CA-125 (cancer antigen 125 [MUC16]) level measurement within 2 weeks before cycle 1. Disease assessment was repeated using the same modalities after cycles 2 and 4 and at the end of the treatment. In patients without signs of disease progression at the end of the treatment, disease assessment was repeated every 8 weeks until disease progression. The clinical response was defined according to World Health Organization (WHO) criteria.26,27 Patients with complete response (CR) according to the WHO criteria in whom CA-125 levels had come to normal were considered to have a complete clinical response. Patients with CR according to the WHO criteria in whom CA-125 levels had not normalized were considered to have a partial clinical response. Patients with progressive disease according to the WHO criteria or with a rise in serum CA-125 levels by > 50% were considered to have disease progression.

Safety was evaluated in accordance with the US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Biochemical parameters were measured on day 1 of each treatment cycle; hematologic parameters were measured weekly until the end of the treatment.

Eligibility Criteria

Eligible patients had advanced ovarian cancer previously treated with only 1 platinum-based chemotherapy regimen. The goal of the limitation of a previous anticancer therapy to only 1 regimen was the intention to reach homogeneity of the population for correct interpretation of long-term results (progression-free survival [PFS] and overall survival [OS]). Patients with increased serum CA-125 levels as the only sign of disease progression were not included. All patients had to be older than 18 years and had to have a performance status of either 0, 1, or 2 according to ECOG (Eastern Cooperative Oncology Group) criteria. Morphologic confirmation of ovarian cancer was required. PFI had to be < 24 months since the last platinum administration. PFI was defined as the time period from the last platinum administration to the disease progression (according to CA-125 level, objective methods of assessment, or both). Patients with PFI < 6 months were considered platinum-resistant. Patients with PFI ≥ 6 months were considered platinum-sensitive. Patients with platelet counts < 100,000 cells/µL, absolute neutrophil counts < 1500 cells/µL, hemoglobin levels < 9 g/dL, inadequate liver function (total bilirubin > 30 µmol/L) or renal function (serum creatinine > 130 µmol/L), or significant cardiovascular diseases with left ventricular ejection fraction < 60% were excluded. Severe concomitant diseases, sensory neuropathy > grade 1, or other malignancies were also criteria for patient exclusion.

Statistical Considerations

The primary endpoint was PFS calculated from the start of investigational therapy to disease progression or the last date of patient contact. Secondary endpoints were OS, objective response rate, and safety. The authors expected to enroll not less than 60% of patients with PFI < 6 months after first-line platinum-based chemotherapy. Analysis of the database of the authors’ department at the N.N. Blokhin Russian Cancer Research Center found that 6-month PFS in this patient cohort was 30%. A 1-stage design was used. With the use of a new regimen, the authors expected to increase 6-month PFS to 55%. To test this hypothesis, 32 patients were needed for accrual with α = .1, power = .9, and a 10% dropout rate. All calculations were done using Statistica software (version 8.0; StatSoft Inc).

Results

From January 2009 to June 2012, 33 patients received treatment in this clinical trial. Patient characteristics are shown in Table 1. Most of the patients had platinum-resistant relapses (63.6%), serous histology (81.9%), and ECOG performance status of 0 or 1 (97%). The time intervals from the last platinum administration to the start of investigational therapy for the entire study group and for patients with platinum-resistant relapses were 6.2 and 5.0 months, respectively.
Objective response could be measured in 29 of 33 patients. The other 4 patients had only unmeasurable lesions. The response rates for the whole group and depending on platinum sensitivity are shown in Table 2.

The response rate for the entire study group was 41.4% (12 of 29), including 7 complete (24.2%) and 5 partial (17.2%) responses. The response rate in platinum-resistant ovarian cancer was lower than in platinum-sensitive disease (54.5% vs. 33.4%), but the difference was not statistically significant ($P = .59$).

The median follow-up time was 17.0 months (range, 4.5-47.3); 47% of patients had died by the time of the present analysis. The median PFS in the whole cohort was 7.4 months (Figure 1). The 6-month and 1-year PFS values were 65.6% and 28.1%, respectively. The median OS was 24.3 months.

There was a difference in PFS between platinum-sensitive and platinum-resistant cancers (10.8 vs. 6.7 months), but it did not reach statistical significance ($P = .14$) (Figure 2A). OS was higher in platinum-sensitive disease (30.4 vs. 18.2 months), which was statistically significant ($P = .02$) (see Figure 2B).

The median number of delivered cycles was 6 (range, 2-8). There were no deaths during the study procedures. One patient was withdrawn after 2 cycles owing to development of acute (M4) leukemia. The most often reported adverse events of chemotherapy are shown in Table 3.

Oxaliplatin and doxorubicin dose reductions were registered in 43.8% and 56.0% of patients, respectively. The main reason for dose reductions was grade 3 or 4 neutropenia, which was reported in 27.5% of cycles. Febrile neutropenia occurred in 2.6% of cycles. Grade 3 or 4 thrombocytopenia occurred in 5.5% of cycles. Despite the use of serotonin receptor 5-HT$_3$ antagonists and dexamethasone prophylaxis, grade 3 or 4 nausea was registered in 6.3% of cycles. Grade 3 or 4 asthenia occurred in 7.3% of cycles. In 9.4% of cases grade 3 neurotoxicity was reported. Other adverse events were mild or moderate in most cases. There were no symptomatic or asymptomatic cardiotoxic events reported in this study.

### Table 1: Patients’ Baseline Characteristics (n = 33)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Median 54</td>
</tr>
<tr>
<td>Range</td>
<td>16-74</td>
</tr>
<tr>
<td>ECOG Performance Status, n (%)</td>
<td>0 13 (39.4%)</td>
</tr>
<tr>
<td></td>
<td>1 19 (57.6%)</td>
</tr>
<tr>
<td></td>
<td>2 1 (3.0%)</td>
</tr>
<tr>
<td>Tumor Histology, n (%)</td>
<td>Serous 27 (81.9%)</td>
</tr>
<tr>
<td></td>
<td>Clear cell 1 (3.0%)</td>
</tr>
<tr>
<td></td>
<td>Mucinous 1 (3.0%)</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma, unspecified 4 (12.1%)</td>
</tr>
<tr>
<td>CA-125 Level Before Chemotherapy, IU/mL</td>
<td>Median 274</td>
</tr>
<tr>
<td></td>
<td>Range 21-3385</td>
</tr>
<tr>
<td>Patients With Prior Taxane-Based Therapy, n (%)</td>
<td>27 (81.9%)</td>
</tr>
<tr>
<td>Platinum-Free Interval</td>
<td>&lt; 6 mo 21 (63.6%)</td>
</tr>
<tr>
<td></td>
<td>6-12 mo 6 (18.2%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 12 mo 6 (18.2%)</td>
</tr>
<tr>
<td>Time From the Last Platinum Adminstration to the Start of Investigational Therapy in the Whole Cohort (mo)</td>
<td>Median 6.2</td>
</tr>
<tr>
<td></td>
<td>Range 0.4-46.9</td>
</tr>
<tr>
<td>Time From the Last Platinum Adminstration to the Start of Investigational Therapy in the Platinum-Resistant Cohort (mo)</td>
<td>Median 5.0</td>
</tr>
<tr>
<td></td>
<td>Range 0.4-15.8</td>
</tr>
</tbody>
</table>

Abbreviations: CA-125 = cancer antigen 125 (MUC16); ECOG = Eastern Cooperative Oncology Group.

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### Table 2: Objective Response Rate With Oxaliplatin/Doxorubicin Combination Therapy

<table>
<thead>
<tr>
<th>Response Type</th>
<th>All Patients</th>
<th>Patients With PFI &lt; 6 mo</th>
<th>Patients With PFI &gt; 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>7 (24.2%)</td>
<td>3 (16.7%)</td>
<td>4 (36.3%)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>5 (17.2%)</td>
<td>3 (16.7%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>12 (41.4%)</td>
<td>8 (44.4%)</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>5 (17.2%)</td>
<td>4 (22.2%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>29 (100%)</td>
<td>18 (100%)</td>
<td>11 (100%)</td>
</tr>
</tbody>
</table>

Abbreviation: PFI = platinum-free interval.

The gold standard chemotherapy for recurrent ovarian cancer has yet to be determined. Platinum-sensitive recurrences require reintroduction of a platinum compound combined with another potentially active cytotoxic agent. In most cases, platinum-resistant recurrences are managed by nonplatinum compounds delivered as monotherapy. However, there is no preferred chemotherapy

### Figure 1: Progression-Free Survival and Overall Survival of the Whole Study Group

Abbreviations: OS = overall survival; PFS = progression-free survival.
regimen, as no regimen has shown greater clinical benefit compared with any other in both platinum-sensitive and platinum-resistant disease.1

The present authors chose an oxaliplatin-based regimen in this clinical trial because (1) oxaliplatin, as a platinum compound, is applicable in the treatment of platinum-sensitive recurrences and because (2) tumors resistant to other platinum compounds do not show complete resistance to oxaliplatin,2 so oxaliplatin can be used in platinum-resistant tumors as well. The inclusion/exclusion criteria allowed enrollment of patients with platinum-sensitive tumors with PFI < 24 months. The authors believe that optimal chemotherapy in recurrent ovarian cancer with PFI > 24 months should be based on carboplatin or cisplatin. Carboplatin- or cisplatin-based chemotherapy in platinum-sensitive tumors with PFI of 6 to 24 months has shown moderate efficacy, with median PFS < 10 months and development of platinum-resistant recurrences in > 50% of cases.28 Therefore, it is important to find different approaches to overcome platinum resistance in such cases.

A large number of trials dedicated to the problem of overcoming platinum resistance by the use of different novel chemotherapy regimens have been performed to date. Some of these trials were based on novel ways of administration of platinum compounds. Investigators from London Imperial College reported on dose-dense and dose-intensive chemotherapy with weekly carboplatin (area under the curve = 3 mg/mL•min) and paclitaxel (70 mg/m²) in platinum-resistant ovarian cancer. This approach showed promising results, with a response rate of 60% and a median PFS of 7.9 months. Median OS was 13 months.29 Ledermann et al (2010)30 evaluated the efficacy of carboplatin/gemcitabine combination therapy in platinum-resistant disease. They found that gemcitabine inhibited reparation of interstrand links in DNA caused by carboplatin. The overall response rate in this study was 29%, and the median PFS and OS were 6.9 and 11.7 months, respectively.

In the present study, in the cohort of platinum-resistant tumors, the response rate was 33.4%, and the median PFS and OS were 6.7 and 18.2 months, respectively. These results are comparable with the outcomes of the aforementioned trials. Of 21 patients with platinum-resistant ovarian cancer, 5 (23.8%) had a PFI after the second-line oxaliplatin/doxorubicin chemotherapy longer than 6 months. These data support the hypothesis of incomplete cross-resistance between oxaliplatin and other platinum agents in solid tumors. The OS rate in the present study was higher than in the aforementioned trials because all patients received investigational therapy in the second-line setting, and a lot of potentially effective drugs were available for them later.

All patients in this study did not have an artificial prolongation of the PFI after the previous platinum-based chemotherapy by administration of nonplatinum regimens. However, this study was limited to the patients with symptomatic recurrences; the patients with elevation of the CA-125 level as the only sign of recurrence

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**Table 3: Safety of Oxaliplatin/Doxorubicin Chemotherapy**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any Grade</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropeniaa</td>
<td>72.3%</td>
<td>27.5%</td>
</tr>
<tr>
<td>Febrile neutropeniaa</td>
<td>2.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12.5%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Anemia</td>
<td>11.7%</td>
<td>0%</td>
</tr>
<tr>
<td>Neurotoxicityb</td>
<td>75.0%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>71.3%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Anemia</td>
<td>54.5%</td>
<td>7.3%</td>
</tr>
<tr>
<td>AST/ALT Elevationc</td>
<td>29.0%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Stomatitisa</td>
<td>2.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Cardiotoxicityb</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Abbreviation: AST/ALT = aspartate transaminase–alanine transaminase ratio.

*aCalculated to number of cycles.

*bCalculated to number of patients.
were not included. Therefore, the median time from the last platinum administration to the start of investigational therapy in the platinum-resistant cohort was 5.0 months (range, 0.4-15.8). The study analyzed how the length of this interval affected the efficacy of chemotherapy, and it was found that the objective response rate (P = 0.1) and PFS (P = .76) did not correlate with the length of this interval in the platinum-resistant cohort.

Patients with platinum-sensitive ovarian cancer had 54.5% of the objective responses, and the median PFS was 10.8 months (range, 0.7-20.2). Only 2 patients developed platinum-resistant recurrences after the second-line oxaliplatin/doxorubicin chemotherapy. Such remarkable results support the authors’ opinion that oxaliplatin/doxorubicin combination therapy is a useful treatment option for platinum-sensitive tumors. These results are comparable with the published data showing that second-line chemotherapy with carboplatin plus gemcitabine, carboplatin plus pegylated liposomal doxorubicin, or carboplatin plus paclitaxel resulted in a median PFS of 8.4 to 11.3 months in platinum-sensitive ovarian cancer.13-32

The toxicity of the oxaliplatin/doxorubicin combination appeared manageable. Unfortunately, the frequency of dose reductions was high. Doses of oxaliplatin/doxorubicin were reduced in 43.8% and 56% of cases, respectively. The reason for dose reductions in most cases was grade 3 or 4 neutropenia. Secondary prophylaxis with granulocyte colony-stimulating factor in patients with severe neutropenia could decrease the rate of dose reductions. The other grade 3 or 4 toxicities included thrombocytopenia, asthenia, and nausea, which occurred in 5.5%, 7.3%, and 6.3% of cycles, respectively. Neurotoxicity was diagnosed in 9.4% of patients. There were no treatment-related deaths. The present investigational regimen is cost-effective owing to the moderate price of oxaliplatin and doxorubicin. Another advantage of this regimen is that patients require hospital visits only once every 3 weeks. Therefore, the authors propose this regimen as a treatment of choice for recurrent ovarian cancer in both developing and developed countries.

Conclusion

The novel chemotherapy regimen for platinum-sensitive and platinum-resistant recurrent ovarian cancer that includes the combination of oxaliplatin/doxorubicin showed promising results in a small group of patients. These results need confirmation in a larger clinical trial.

Clinical Practice Points

- There are no gold standards of chemotherapy for both platinum-sensitive and platinum-resistant recurrent ovarian cancer. Oxaliplatin and doxorubicin seem to be active drugs in recurrent ovarian cancer but nowadays are rarely used for this indication.
- This study found that the investigational combination of oxaliplatin/doxorubicin is active in both platinum-sensitive and platinum-resistant ovarian cancer. The objective response rate and PFS in the platinum-resistant cohort were comparable with the best results published in the literature.
- The toxicity profile of the oxaliplatin/doxorubicin combination appeared manageable. This regimen is cost-effective owing to the acceptable price of oxaliplatin and doxorubicin. Another advantage of this regimen is the need for hospital visits only once every 3 weeks.

Acknowledgments

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Disclosure

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References