Abstract. Background: The role of combination chemotherapy regimens in the management of ovarian cancer patients with tumors previously exposed to platinum compounds and paclitaxel has not yet been defined. The present phase II study evaluated the activity and toxicity of a gemcitabine-ifosfamide-cisplatin combination in the aforementioned group of patients. Given the in vitro and in vivo synergism between the three agents, it was believed that using a three-drug combination would overcome tumor resistance to cisplatin. Patients and Methods: Twenty-four patients were enrolled in the study. The median age was 56 years and the median performance status 1. Eight (34%) had potentially platinum-sensitive, 6 (24%) had primary platinum-resistant and 10 (42%) patients had secondary platinum-resistant tumors. Treatment consisted of gemcitabine 1 g/m² i.v. on days 1 and 8, cisplatin 75 mg/m² i.v. over 2 h fractionated over days 8 and 9, and ifosfamide 5 mg/m² i.v. over 1 h fractionated on days 8-9 with mesna uroprotection. Courses were administered every 3 weeks on an outpatient basis. Granulocyte colony-stimulating factor (G-CSF) was given at a dose of 5 μg/kg/day on days 10-14. A median of 4 cycles were administered with the delivered dose intensity at 85% of the planned dose for the three agents. Results: Among 24 patients evaluable for response and toxicity, there were 8 partial responses with a response rate of 33% (95% confidence interval 16.4-55%). Stable disease was recorded in 6 (25.7%) and progressive disease in 10 (42%) patients. Subgroup analysis revealed a response rate of 50% in potentially platinum-sensitive, 16.5% in primary platinum-resistant and 30% in secondary platinum-resistant tumors. The median response duration was 5 months (range 3-12 months), the median time to progression 6 months (range 3-16 months) and the median survival 12 months (range 3-24 months). Myelotoxicity was significant, with neutropenia grade 3 and 4 occurring in 35% and 20% of patients, respectively. Four episodes (3.5% of all cycles) of febrile neutropenia were documented and were well managed with oral antibiotics and G-CSF continuation until complete recovery. Grade 1, 2 and 3 peripheral neuropathy developed in 40%, 30% and 10% of patients, respectively. Conclusion: The three-drug combination demonstrated a significant effectiveness in potentially platinum-sensitive tumors and a moderate efficacy in platinum-resistant tumors. The regimen, although myelotoxic, is tolerable with G-CSF support. Further investigation via comparative studies is required to define any superiority of the present regimen over doublets of the three agents in this group of patients.

Chemotherapy remains the main treatment modality for the majority of patients with ovarian carcinoma. Despite the high response rate and the prolonged median survival time observed with the standard front-line chemotherapy, which currently is a combination of a platinum agent and paclitaxel, over 80% of patients relapse requiring further treatment (1, 2). Recurrent disease is classified as being either sensitive or resistant to platinum compounds according to the time elapsed from the last chemotherapy cycle and the disease relapse (3). Retreatment with cisplatin or carboplatin offers a response rate of 30%, when the disease is considered potentially platinum sensitive (4). For platinum-resistant disease, chemotherapy relies on other chemotherapeutic agents. Therefore, an important goal of investigative effort in ovarian cancer is the identification of agents or drug combinations that are active in platinum-resistant disease and that may be used as salvage chemotherapy.
Patients and Methods

Patient population. Patients were required to have: a) histologically confirmed epithelial ovarian carcinoma with manifestations of locoregional or metastatic bidimensionally measurable disease; b) either primary tumors resistant (non-responding or progressing) to platinum-based combinations or recurring within 6 to 12 months from previous platinum-based treatment; c) paclitaxel as part of their prior chemotherapy regimen. Other eligibility criteria included: a life expectancy of at least 3 months, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2, age ≤75 years, hematological parameters and blood chemistry indicating normal organ function (absolute neutrophil count (ANC) ≥1.5 × 10⁹ g/l, platelet count ≥100 × 10⁹ g/l, hemoglobin ≥10 g/dl, normal total bilirubin, (aspartate amino transferase) AST ≤2.5 times the upper limit of normal value (ULN), alkaline phosphatase ≤6 × ULN and creatinine clearance ≥60 ml/min). Exclusion criteria included: sensitivity to platinum, or a previous chemotherapy regimen that did not contain platinum. Patients were excluded from the study if there was a history of prior malignancies, concurrent infection, pre-existing diarrhea, intestinal paralysis or obstruction. The study was approved by the Ethics and Scientific Committees of the participating centers and all patients gave their informed consent in order to participate in the study.

Treatment plan. Eligible patients were treated as follows: gemcitabine was administered at 1 g/m² intravenously over 30 minutes on days 1 and 8. Ifosfamide was administered at 5.0 g/m² intravenously over 1 h, fractioned over 2 days (days 8 and 9) together with mesna uroprotection, 40% of the ifosfamide dose, given intravenously before, at 3 and 6 h after ifosfamide. Cisplatin was administered at 75 mg/m² i.v. over 2 h fractionated over 2 days (days 8 and 9) with adequate vigorous pre- and posthydration, mannitol and furosemide diuresis, and electrolyte replacement: 20 mEq potassium chloride and 8 mEq magnesium sulfate per liter of posthydration solution [0.9% normal saline (NS) or 0.5 NS + 5% dextrose (D5/w)].

Supportive care. The regimen was administered every 3 weeks for a maximum of 6 cycles unless there was evidence of disease progression, unacceptable toxicity or patient refusal. Standard antiemetic medication included ondansetron 24 mg i.v. 1 h before chemotherapy. Dexamethasone 20 mg i.v. was administered 1 h before chemotherapy (days 1, 8 and 9). Hematopoietic growth factors included G-CSF (lenogastim) 5 μg/kg s.c. from day 10 to day 14.

Dose modifications. The prerequisites for dose modifications were set as follows: i) any episode of grade 4 neutropenia of longer than 7 days’ duration, ii) any episode of febrile grade 3 or higher neutropenia, iii) any episode of grade 4 thrombocytopenia requiring platelet transfusions, iv) any nonhematological grade 3 or 4 toxicity excluding nausea and vomiting, musculoskeletal and arthritic pain (myalgia/arthritis syndrome). The following guidelines were applied with respect to dose reductions for toxicity: i) For neutropenia, meeting the aforementioned criteria, cisplatin, and ifosfamide doses were reduced by 20% in subsequent cycles, and if toxicity reappeared after a total of 40% reduction from the starting dose in consecutive cycles, treatment was withdrawn; however, the patient was evaluable for toxicity and response; ii) For thrombocytopenia, a reduction of cisplatin by 20% was applied in addition to gemcitabine and ifosfamide dose reductions as specified for neutropenia; iii) For neuropathy grade 3 or higher, treatment was interrupted; iv) For renal toxicity grade 3 or higher toxicity (serum creatinine elevations, >3 × normal) treatment was withheld until recovery (serum creatinine, <1.8 mg/dl) with cisplatin and ifosfamide administered with more posthydration, mannitol diuresis, and hospitalization in subsequent cycles. If the glomerular filtration rate dropped to <40 ml/min, cisplatin and ifosfamide were omitted in subsequent cycles. However, no dose reductions or schedule modification were required for renal toxicity in any patient on the study; v) For grade 3 or higher central nervous system (CNS) toxicity (ifosfamide encephalopathy), the dose of ifosfamide was reduced by 20%, and more hydration with bicarbonates was anticipated in subsequent cycles. Where encephalopathy reappeared, then ifosfamide was omitted from subsequent cycles. Where blood counts had not recovered to ANC ≥1,500/μl and platelet count ≥100,000/μl on the day of therapy, treatment was withheld until recovery and after a maximum delay of 2 weeks, no further therapy was administered in cases in which counts did not return to normal.

Patient evaluation. Baseline evaluations included: patient history, physical examination, chest X-rays, complete blood count with differential and platelet count, standard blood chemistry and ECG. Computed tomography (CT) scans of the chest, abdomen, pelvis
Tumor evaluation and criteria for response. Tumor response was assessed after every 2 cycles using the World Health Organization (WHO) response criteria (17). An independent radiologist reviewed all tumor responses. Response duration was calculated from the day on which at least a 50% reduction in tumor volume was documented until the first documentation of progressive disease. Time to tumor progression (TTP) was calculated from the first day of drug administration to the first documentation of tumor progression. Overall survival was measured from the date of first drug administration to death. Patients without progression who died during the study were considered treatment failures.

Monitoring for toxicity. Toxicity evaluations were graded according to National Cancer Institute (NCI) common toxicity criteria (17). Hematological and clinical chemistry parameters were measured at baseline and then at least weekly throughout treatment. Liver function was monitored at each cycle.

Statistical methods. The primary objective of the study was the overall response rate (RR). All analyses were based on the intent to treat population. Confidence intervals (CI) for response rates were calculated according to the method described by Simon (18). Simon’s two-stage mini-max design was used to allow for early termination of the trial in the event of a poor response rate. An optimized two-stage plan for accrual was used at a first-stage design with 16 patients. It was calculated that with an anticipated RR of approximately 30% (minimum level of activity to be of interest), the sample size required for having confidence limits of ±8% would be 32 patients. The survival distributions for response duration, TTP and overall survival were estimated using the Kaplan-Meier method. Dose intensity was expressed in mg/m²/week.

Results

Patient characteristics. From June 2004 to September 2007, 24 patients were enrolled and their characteristics are listed in Table I. Eight patients had received carboplatin plus cyclophosphamide as first-line chemotherapy and when their tumors recurred with a TTP between 6 and 12 months, they were placed on paclitaxel plus carboplatin. Sixteen patients had received paclitaxel and carboplatin as first-line chemotherapy and had relapsed after brief initial response in less than 6 months (6 patients) or had stable or progressive disease upon completion of treatment (10 patients). A total of 124 chemotherapy cycles were administrated, with a median of 4 cycles per patient (range 3-6).

Response and survival data. All 24 patients were assessable for response and toxicity. The efficacy of the regimen is presented in Table II. Responses were observed in all sites of disease, such as liver (n=2 patients), lymph nodes (n=2 patients) and intra-abdominal disease (n=4 patients).

Compliance with treatment. A total of 8 treatment cycles (6%) were delayed for 3-14 days (median 7 days), mainly as a result of patient choice due to difficulties in traveling from district areas (2 cycles) and 6 cycles due to neutropenia on the day of treatment. The delivered dose intensity was 85% of the planned dose for the three agents due to delays and dose reductions.
Toxicities. Hematological and non-hematological toxicities encountered in the present study were evaluated in all patients and cycles, and are presented in Tables III and IV, respectively. Grade 3 and 4 toxicities included neutropenia in 35% and 20% of patients respectively, with 4 cases (3.2% ) of all administered cycles developing febrile episodes well managed with oral antibiotics in the outpatient setting. Grade 3 thrombocytopenia developed in 40%. Grade 1 to 2 CNS toxicity due to ifosfamide was observed in 3 patients (12% ) and was rapidly reversible. No renal toxicity was observed. Neurotoxicity was common with 40%, 30% and 10% developing grade 1, 2 and 3, respectively.

Discussion

Despite the high response rate achieved with the standard chemotherapeutic agents, a great percentage of patients with ovarian cancer require salvage chemotherapy upon recurrence. Theoretically, in order to establish an effective second-line chemotherapy, it is important to use either non-cross resistance agents after the initial regimen, or a combination of drugs with synergistic effect aiming to overcome tumor resistance. Chemotherapy agents active in other tumor types have subsequently been explored in patients with ovarian cancer. Ifosfamide as single agent has shown activity in a small percentage of patients with ovarian tumors refractory to the old cisplatin-cyclophosphamide regimen (5-7). Responses have also been documented with ifosfamide in ovarian cancer patients carrying tumors not responding to cisplatin-paclitaxel regimen (8-10). The interest in ifosfamide as an alternative agent has grown again most recently. Ifosfamide is being combined either with epirubicin with a response rate of 23% (19), or with pegylated liposomal doxorubicin with a 14% response rate and a 35% stable disease (20). In another study, monotherapy with ifosfamide as salvage agent achieved a 19% response rate with documented pathological complete responses followed by long-term survival (21). However, ifosfamide has been shown to synergize with platinum compounds by reversing intracellular mechanisms of resistance that ultimately would lead to increased DNA repair and/or detoxification of reactive intermediates of cisplatin, such as the glutathione/thiol systems. Depletion of the intracellular glutathione pool by 70% has been observed in peripheral blood lymphocytes after ifosfamide administration (22). It thus is theoretically conceivable that the administration of ifosfamide and cisplatin might overcome resistance to cisplatin due to elevated glutathione concentrations.

In the present study, cisplatin and ifosfamide were combined with gemcitabine an agent known to have efficacy in ovarian cancer (12-14). Gemcitabine as single agent was administered recently in heavily pretreated patient with ovarian cancer. In a Japanese study, the response rate was 18%, with grade 3-4 39% granulocytopenia and 10% thrombocytopenia (23). The drug was given in another study at a fixed dose rate with responses similar to that achieved using 30 min infusion but with higher toxicity (24). Combinations of gemcitabine with several other agents have been applied in pretreated patients with ovarian cancer. In two studies, gemcitabine was combined with pegylated liposomal...
doxorubicin as salvage regimen (25) and as an alternating combination with cisplatin and cyclophosphamide (26) in pretreated patients. In both studies, the results were encouraging with moderate toxicity. Another gemcitabine combination for pretreated ovarian cancer patients was its co-administration with oxaliplatin, yielding 18.5% and 35% response rates in platinum-resistant and platinum-sensitive patients respectively, with the major toxicity being thrombocytopenia (27). The toxicity observed in the present study with the application of the three agents was moderate. Despite the high incidence of grade 3 and 4 neutropenia, it can be stated that this was rarely prolonged (>5 days) and therefore patients were unlikely to be exposed to the danger of febrile neutropenia. The 3.5% incidence of febrile neutropenia does not appear excessive and is probably comparable to the levels observed in other studies applying combinations of newer agents (taxanes, vinorelbine, gemcitabine and irinotecan) with cisplatin or carboplatin (28-30). Moreover, all febrile-neutropenic patients in the current study were managed successfully as outpatients with broad-spectrum antibiotics, and their pyrexia was of up to 3 days’ duration. Other toxicities did not appear to be significant in the current study. The very low incidence of severe grade 3 peripheral neuropathy in our study might be explained by the fact that the patients had received carboplatin in the past and the dose of cisplatin was only 75 mg/m².

The regimen applied in the present study resulted in a moderate response rate of 33%. As expected, according to subgroup analysis, patients with potentially platinum-sensitive tumor had a higher response rate (50%), followed by the 30% response rate of patients with secondary platinum-resistant tumors. Unfortunately, it seems that the synergistic effect of the combination applied in the present study could not overcome the primary cisplatin-resistance, resulting in a poor 16.5% response rate in this group of patients. Overall, the response rate is within the range of these achievable by single agents or two-drug combinations registered in the second-line setting for the treatment of ovarian tumors (16, 28-30).

Conclusion

Patients with primary cisplatin resistance face serious problems. Even with the application of novel non-platinum agents in this group of patients, the achieved response rates are very low. Salvage treatment with the present regimen demonstrated a significant effectiveness in patients with potentially platinum-sensitive tumors. The efficacy of this three-drug combination in patients with platinum-resistant tumors was moderate. The regimen, although myelotoxic, was well tolerated with G-CSF support. Further studies where doublets could be compared with a three-drug combination regimen are warranted.

References


Received February 4, 2009
Revised May 18, 2009
Accepted May 21, 2009