Paclitaxel-Ifosfamide-Cisplatin as Salvage Chemotherapy in Ovarian Cancer Patients Pretreated with Platinum Compounds and Paclitaxel

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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 paclitaxel-ifosfamide-cisplatin combination in the aforementioned group of patients. Given the in vitro and in vivo synergism between these three agents, it was believed that using a three drug combination would overcome tumor resistance to cisplatin. Patients and Methods: Thirty-five patients were enrolled in the study. The median age was 55 and the median performance status 1. Thirteen (37%) had potentially platinum sensitive, 12 (35%) had primary platinum-resistant and 10 (28%) patients had secondary platinum-resistant tumors. Treatment consisted of paclitaxel 175 mg/m^2 as a 3 h i.v. infusion on day 1, cisplatin 75 mg/m^2 i.v. over 2 h fractionated over days 1 and 2, and ifosfamide 5 mg/m^2 i.v. over 1 h fractionated on days 1-2 with mesna uroprotection. Courses were administered every 3 weeks on an outpatient basis. Granulocyte-colony stimulation factor (G-CSF) was given at a dose of 5 μg/kg/day on days 4-10. A median of 4 cycles were administered with the delivered dose intensity at 85% of the planned dose for the three agents. Results: Among 35 patients evaluable for response and toxicity, there were 10 partial responses with a response rate of 28.6% (95% confidence interval 12%-45%). Stable disease was recorded in 9 (25.7%) and progressive disease in 16 (45.7%) patients. Subgroup analysis revealed a response rate of 38.5% 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 3-14 months), the median time to progression 6 months (range 3-18 months) and the median survival 12 months (range 3-44 months). Myelotoxicity was significant with neutropenia grade 3 and 4 occurring in 35% and 45% of patients, respectively. Eight episodes (5% of all cycles) of febrile neutropenia were documented and well managed with oral or i.v. antibiotics and G-CSF continuation until complete recovery. Grade 1, 2 and 3 peripheral neuropathy developed in 30%, 30% and 10% of patients, respectively. In 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 cancer. 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 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

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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.

Ifosfamide, an oxazophosphorine alkylating agent, has shown activity in 10% to 20% of patients with platinum refractory tumors (5-7). A modest activity of ifosfamide was also documented in ovarian carcinoma patients with tumors resistant to a platinum paclitaxel regimen resulting in a response rate of 10%-20% (8-10). Ifosfamide displays synergism with platinum derivatives in animal models and lacks cross resistance with cyclophosphamide in a number of tumors, including ovarian cancer (11). In addition, *in vitro* synergism has been documented between paclitaxel and the activated ifosfamide metabolite against cisplatin-resistant ovarian carcinoma cell lines (12). Based on these data, a prospective phase II study was conducted to evaluate the efficacy and toxicity of a cisplatin-paclitaxel-ifosfamide regimen as salvage treatment in ovarian cancer patients whose tumors have been exposed both to cisplatin and paclitaxel. Combination of ifosfamide with paclitaxel and cisplatin has been performed in a previous phase I study in several tumors by our group in the outpatient setting and it has been demonstrated that high individual doses of each drug can be achieved aided by granulocyte-colony stimulating factor (G-CSF) support with acceptable toxicity (13). Preliminary results of this regimen in ovarian cancer were presented in an abstract form at the ASCO meeting of 1998 (14).

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 the 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 ≥1.5x10 q/L, platelet count ≥100x10 q/L, hemoglobin ≥10 g/dL, normal total bilirubin, AST ≤2.5 times the upper limit of normal value (ULN), alkaline phosphatase ≤6x 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, preexisting 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: premedication, consisting of dexamethasone 20 mg, dimethindene maleate (Fenistil) 4 mg and ranitidine 50 mg, was administered intravenously 1 h before paclitaxel (Taxol®) which was then administered at 175 mg/m^2 over 1 h by intravenous infusion on day 1 (13). Ifosfamide was administered at 5.0 g/m^2 intravenously over 1 h fractioned over 2 days 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/m^2 *i.v.* over 2 h fractionated over 2 days 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, at 12 h 8 mg *per os* on days 1 and 2, and post-chemotherapy 8 mg 3 times a day *per os* on days 3-5. Dexamethasone 20 mg *i.v.* was administered 1 h before chemotherapy (day 1 as paclitaxel premedication also) on days 1 and 2, and post-chemotherapy 4 mg 3 times daily or methylprednisolone 16 mg twice daily *per os* on days 3-5. Hematopoietic growth factors included G-CSF (lenograstim) 5 μg/kg *s.c.* from day 4 to day 10.

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/arthalgia syndrome). The following guidelines were applied with respect to dose reductions for toxicity: i) For neutropenia, meeting the aforementioned criteria, paclitaxel, 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 paclitaxel and ifosfamide dose reductions as specified for neutropenia; iii) For grade 3 or higher mucositis, the doses of paclitaxel and ifosfamide were reduced by 20% in subsequent cycles; iv) For neuropathy grade 3 or higher, treatment was interrupted; v) For renal toxicity grade 3 or higher toxicity (serum creatinine elevations >3x 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; vi) 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 ≥1500/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 and whole body bone scintigraphy were performed at study entry and CT scan of the brain whenever clinically indicated. Complete blood counts with differential and platelet counts were performed twice weekly or daily in case of grade 3/4 neutropenia, thrombocytopenia or febrile neutropenia until hematological recovery; blood chemistry and physical examination were performed every 3 weeks. Patients were evaluated before each cycle for lesions assessable by physical examination. Pelvic examination was performed at baseline and after 3 and 6 cycles. All patients were evaluated by the appropriate imaging studies indicative of the measurable target lesions every 2 chemotherapy cycles.

Tumor evaluation and criteria for response. Tumor response was assessed after every 2 cycles using the World Health Organization (WHO) response criteria (15). 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 (15). 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. 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 (16). 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 activiy to be of interest) the sample size required for having confidence limits of ±8% would be 32 patients. The survival distributions for response duration, time to progression (TTP) and overall survival were estimated using the Kaplan-Meier method. Dose intensity was expressed in mg/m^2/week.

Results

Patient characteristics. From June 1996 to September 2002, 35 patients were enrolled and their characteristics are listed in Table I. Thirteen patients had received carboplatin plus cyclophosphamide as first-line chemotherapy and when their tumors recurred with a time to progression between 6 and 12 months they were placed on single agent paclitaxel. Twenty-two patients had received paclitaxel and carboplatin as first-line chemotherapy and had relapsed after brief initial response in less than 6 months (10 patients) or had stable or progressive disease upon completion of treatment (12 patients). A total of 162 chemotherapy cycles were administered with a median of 4 cycles per patient (range 2-6).

Table I. *Patient characteristics.*

	Patients	%
Eligible patients	35	100
Age (years)		
Median Range	55 (38-65)	
Performance Status (ECOG)		
0	18	52
1	13	37
2	4	11
Stage (FIGO)		
IIIc	25	72
IV	10	28
Tumor histology		
Serous	21	60
Endometrioid	4	12
Mucinous	3	8
Adenocarcinoma	3	8
Mixed	4	12
Tumor Grade		
1	5	14
2	10	28
3	17	50
Unknown	3	8
Involved sites		
Omentum-mesentery-ascites	28/18	80/52
Pelvic-retroperitoneal-lymph nodes	10	28
Liver	9	26
Pleura	9	26
Prior chemotherapies		
Carboplatin+cyclophosphamide followed by paclitaxel upon early recurrence	13	37
Carboplatin+paclitaxel		
a) Brief initial response and early recurrence	10	28
b) Stable or progressive disease early recurrence	12	35
Interval from previous chemotherapy treatment (months)		
Median	3	
Range	2-4	
GOG standard criteria		
Potentially platinum-sensitive	13	37
Primary platinum-resistant	12	35
Secondary platinum-resistant	10	28

Response and survival data. All 35 patients were assessable for response and toxicity. The efficacy of the regimen is

Table II. *Clinical response to treatment.*

	N	% of all patients (n=35)
Complete response	–	–
Partial response	10	28.6 (95% CI 12%-45%)
Stable disease	9	25.7
Progressive disease	16	45.7
Responses according to GOG criteria		
Potentially platinum-sensitive	5/13	38.5
Primary platinum-resistant	2/12	16.5
Secondary platinum-resistant	3/10	30

CI: confidence interval; median duration of response 5 (3-14) months; median time to progression 6 (3-18) months; median survival 12 (3-44) months.

Table III. *Hematological toxicity (NCI-CTC Grade).*

	NCI-CTC grade (% of patients, all cycles)			
Toxicity	1	2	3	4
Leukopenia	15	20	40	25
Neutropenia	5	15	35	45
Thrombocytopenia	35	25	12	–
Anemia	40	20	15	–
Febrile neutropenia 8 episodes= 5% of all cycles				

NCI: National Cancer Institute; CTC: Common Toxicity Criteria.

Table IV. *Nonhematological toxicities (NCI-CTC Grade).*

	NCI-CTC grade (% of patients, all cycles)			
Toxicity	1	2	3	4
Nausea-vomiting	65	30	25	–
Mucositis	30	–	–	–
Myalgia/arthralgia	50	40	3	–
Neurologic				
Peripheral	30	30	10	–
CNS	20	8	–	–
Alopecia	–	100	–	–
Renal	5	5	–	–
Hematuria	5	-	–	–

NCI= National Cancer Institute; CTC= Common Toxicity Criteria.

presented in Table II. Responses were observed in all sites of disease, such as liver (n=2 patients), lymph nodes (n=6 patients) and intra-abdominal disease (n=8 patients).

Compliance with treatment. A total of 16 treatment cycles (10%) were delayed for 3-14 days (median 7 days) mainly as a result of patient choice due to difficulties in traveling from district areas (8 cycles) and 8 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 45% of patients respectively, with 8 cases (5%) of all administered cycles developing febrile episodes well managed with oral antibiotics in the outpatient setting (4 episodes) or with *i.v.* antibiotics (4 episodes). Grade 3 thrombocytopenia developed in 3 patients (12%). Grade 1 to 2 CNS toxicity due to ifosfamide was observed in 10 patients (28%) and was rapidly reversible. No renal toxicity was observed. Myalgias and arthralgias, mainly caused by paclitaxel, were common but not severe. Neurotoxicity was common with 30%, 30% and 10% developing grade 1, 2 and 3, respectively.

Discussion

Despite the high response rate achieved with the standard chemotherapeutic agents, a high 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. 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 non-responsive to the cisplatin-paclitaxel regimen (8-10). The interest in ifosfamide as an alternative agent in previously treated patients has grown. Ifosfamide is being combined either with epirubicin, with a response rate of 23% (17), or with pegylated liposomal doxorubicin, with a 14% response rate and 35% stable disease (18). In another study, monotherapy with ifosfamide as salvage agent achieved a 19% response rate with documented pathological complete responses followed by long-term survival (19). As a three-drug combination, the regimen applied in the present study is interesting because of its significant pharmacokinetic and synergistic properties. Several groups have demonstrated in the past that paclitaxel intensifies the cell-killing effects of chemically induced DNA damage brought about by alkylating agents and cisplatin, provided that paclitaxel precedes these agents (20). In the clinical setting,

paclitaxel has shown enhanced activity and possibly synergistic effects when combined with alkylating agents such as cyclophosphamide/ifosfamide (21) or cisplatin (22). However, ifosfamide has 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 (23). It thus is theoretically conceivable that the administration of ifosfamide and cisplatin might overcome resistance to cisplatin due to elevated glutathione concentrations.

In a very interesting study by Gercel-Taylor *et al.* it was shown that the colonies of ovarian cancer had a higher chance of becoming mutated and chemoresistant to cisplatin than to paclitaxel or topotecan (24). Therefore, given the *in vitro* and *in vivo* synergism of pairs of drugs between paclitaxel, ifosfamide, and cisplatin, it is expected that the three-drug combination would exert a favorable cytotoxicity profile against cisplatin-resistant ovarian tumors.

The rationale of combining paclitaxel, ifosfamide and cisplatin derives from both *in vitro* data and theoretic assumptions based on the properties of each individual cytotoxic agent which mediate the cellular damage it brings about. In brief, paclitaxel inhibits the energy dependent enzymatic reactions by disengaging activated intracellular phosphate (*e.g.* ATP and GTP) required for the repair of the DNA damage induced by cisplatin (causing kinking of the DNA double helix) and oxazaphosphorine (cyclophosphamide and ifosfamide) alkylating agents (prevention of DNA strand separation and unwinding). The different types of DNA damage caused by cisplatin and oxazaphosphorine cytostatics are repaired by the nucleotide excision repair and the mismatch repair pathways (25).

Establishment of the recommended dose for phase II testing was based on our previous phase I study (5). In our previous phase I study and the current study, it was anticipated that paclitaxel, ifosfamide and cisplatin can be combined at considerably high individual doses with acceptable toxicity and ease of administration in the outpatient setting aided by G-CSF support. 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 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 (26, 29). Moreover, most febrile-neutropenic patients (4 of 8) 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. Only grade 2 myalgia/arthralgia after paclitaxel administration was encountered. Neurotoxicity is of major concern particularly with paclitaxel/cisplatin combinations and appears to constitute the dose-limiting factor when dose escalation is facilitated by G-CSF, as shown in the study of Rowinsky *et al.* (19). In this landmark analysis of neurotoxicity, it became apparent that peripheral neuropathy was cumulative in nature and evident after four to six cycles. Cisplatin seems to aggravate the neuropathy caused by paclitaxel because combinations of carboplatin and paclitaxel have shown a very limited degree of peripheral neuropathy. Moreover, cisplatin on its own has demonstrated a dose-dependent neurotoxicity profile with most episodes occurring at doses $\geq$100 mg/m^2. The very low incidence of severe grade 3 peripheral neuropathy in our study might be explained by the fact that we did not exceed 175 mg/m^2 of paclitaxel combined with 75 mg/m^2 of cisplatin compared with the study of Rowinsky *et al.* (19) in which neurotoxicity was dose-limiting at 250 mg/m^2 of paclitaxel.

The regimen applied in the present study resulted in a moderate response rate of 28.6%. As expected, according to subgroup analysis, patients with potentially platinum-sensitive tumors had a higher response rate (38%), followed by the 28.5% 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% response rate in this group of patients. Overall the response rate is within the range of response rates achievable by single agents or two-drug combinations registered in the second-line setting for the treatment of ovarian tumors (26-29). Nevertheless, the three-drug combination has also been administered as first-line chemotherapy in ovarian cancer in a Greek study obtaining an objective response rate of 85% and an overall survival of 52.8 months (30). In a recent study, the three-drug combination was given as first-line treatment (paclitaxel and cisplatin intraperitoneally and ifosfamide *i.v.*) yielding an impressive 81% response rate and a 53 month median survival (31).

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 ifosfamide can be combined in with cisplatin or paclitaxel, the latter administered either *i.v.* or intraperitoneally, are warranted.

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