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Dose-dense cisplatin/paclitaxel: a well-tolerated and highly effective chemotherapeutic regimen in patients with advanced ovarian cancer

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Abstract

A randomised phase I/II trial with weekly cisplatin 70 mg/m^2 (days 1, 8, 15, 29, 36, 43) in combination with escalating doses of paclitaxel either 4-weekly or weekly was conducted in 49 patients with ovarian cancer; patients were chemotherapy-naïve or had a first relapse after platinum-based chemotherapy. Paclitaxel could be safely escalated to 225 mg/m^2 4-weekly or 100 mg/m^2 weekly, with fatigue as the major adverse event. Myelosuppression, renal toxicity and neurotoxicity were mild to moderate. Pharmacokinetic analysis showed an approximately 2-fold reduction of DNA-adduct formation in leucocytes compared with cisplatin without paclitaxel. No pharmacokinetic interaction was found between paclitaxel and cisplatin. After (re-)induction, additional chemotherapy consisted of conventional paclitaxel/cisplatin, paclitaxel/carboplatin, paclitaxel single agent or carboplatin/cyclophosphamide. The overall response rate was 94% in 17 evaluable chemotherapy-naïve patients and 84% in 25 patients with recurrent disease. Median progression-free survival (PFS) was 17 months (chemotherapy-naïve: 23 months, recurrent: 11 months) and median overall survival was 41 months (chemotherapy-naïve: 48 months, recurrent: 24 months). In conclusion, both cisplatin/paclitaxel regimens showed excellent activity with manageable toxicity in patients with advanced ovarian cancer.

Keywords: Cisplatin; Paclitaxel; Weekly chemotherapy; Ovarian cancer; Dose intensity; Pharmacokinetics; Toxicity; Response

1. Introduction

Ovarian carcinoma is the most lethal of gynaecological malignancies [1]. Most patients have advanced disease at presentation and cannot be cured by surgery alone. Here, the standard of care consists of surgical debulking and platinum-based combination chemotherapy. The recommended first-line chemotherapy is 3-weekly administration of paclitaxel with cisplatin or carboplatin [2]. Two large phase III trials demonstrated a clinical response rate of 59–73% with a median time to progression of 15.5–18 months and median overall survival of 35–38 months [3,4]. However, pathological complete remission is obtained in only a few patients and most patients with advanced disease will eventually have disease progression and die. Although salvage chemotherapy may result in secondary remissions with relief of symptoms and improvement in the quality of life, relapse is universal with a median progression-free survival of less than 1 year [5–9]. Significant improvement in the management of ovarian cancer can only be expected from novel treatment strategies. In the absence of new agents with improved activity against ovarian cancer, the administration of cisplatin and paclitaxel in a dose-dense manner could be an attractive option. We previously demonstrated the feasibility of cisplatin 70 mg/m^2 weekly in combination with oral etoposide in patients with advanced ovarian cancer [10]. In the present study, we examined an induction regimen with cisplatin 70 mg/m^2 weekly in combination with escalating doses of paclitaxel administered either weekly or once every 4 weeks. Major goals of the study were (1) to determine the maximum tolerated dose (MTD) of

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paclitaxel in both regimens, (2) to describe and quantify the haematological and non-haematological toxicities, (3) to study pharmacodynamic and pharmacokinetic aspects, (4) to assess antitumour response, progression-free survival and overall survival, and (5) to determine which regimen is the most feasible for further study.

2. Patients and methods

2.1. Eligibility

Patients were required to have histologically-confirmed advanced ovarian or fallopian tube cancer and scheduled to receive platinum-based chemotherapy. No prior therapy with paclitaxel and no more than one prior platinum-based chemotherapy regimen were allowed. Patients should not have received extensive radiotherapy within 4 weeks before study entry; indicator lesions must not have been irradiated. Other eligibility criteria included WHO performance status $\leqslant 2$, peripheral neuropathy $\leqslant$grade 1, white blood cell count (WBC) $\geqslant 3000\times10^6$ cells/l, absolute neutrophil count (ANC) $\geqslant 1500\times10^6$ cells/l, platelet count $\geqslant 100\times10^9$ cells/l, total bilirubin 1.25× upper limit of normal, serum transaminases $\leqslant\times 2$ (in case of liver metastases $\leqslant 3\times$) the upper limit of normal, serum creatinine $\leqslant 120$ μmol/l (or creatinine clearance $\geqslant 50$ ml/min) and no signs of bowel obstruction. Excluded were patients with brain or leptomeningeal involvement, significant neurological or psychiatric disorders, uncontrolled hypertension, arrhythmia, angina pectoris, congestive heart failure, active infection, peptic ulcer, unstable diabetes mellitus or other contraindications for the use of corticosteroids. Ascites or pleural effusions with an estimated amount of more than one litre had to be evacuated before entry into the treatment protocol. Written informed consent was obtained from each patient. The study was approved by the Research Ethics Committee of the University Hospital, Rotterdam.

2.2. Study treatment

Paclitaxel was supplied as a concentrated sterile solution with 6 mg/ml in a 5-ml vial in 50% polyoxyethylated castor oil (Cremophor EL) and 50% dehydrated alcohol. The drug was administered by continuous intravenous (i.v.) infusion in 500 ml normal saline (NaCl 0.9% w/v) over 3 h. All patients received premedication with dexamethasone 10 mg, clemastine 2 mg and ranitidine 50 mg i.v. 30 min before the paclitaxel infusion. Cisplatin powder was dissolved in 250 ml hypertonic saline (NaCl 3% w/v) and administered by i.v. infusion over 3 h. All patients were prehydrated with 1 l normal saline over 4 h. Thirty minutes before the cisplatin infusion ondansetron 8 mg was administered i.v. When cisplatin administration was not preceded by paclitaxel, dexamethasone 10 mg was given together with ondansetron as antiemetic prophylaxis. After cisplatin infusion, patients were posthydrated with at least 3 l dextrose 5% (w/v) and normal saline supplemented with potassium chloride (20 mmol/l) and magnesium sulphate (2 g/l). Ondansetron 8 mg in combination with dexamethasone 3 mg twice daily by mouth on days 2–3 was prescribed as prophylaxis for delayed nausea and vomiting.

The intended induction treatment consisted of cisplatin 70 mg/m^2 on days 1, 8 and 15 (cycle 1) and days 29, 36 and 43 (cycle 2). The administration of cisplatin was preceded by paclitaxel either every 4 weeks on days 1 and 29 (regimen A) or weekly on days 1, 8, 15, 29, 36 and 43 (regimen B). Patients were randomly assigned to regimen A or B. Paclitaxel doses were escalated according to a pre-established schedule without the use of haematopoietic growth factors. Dose levels of paclitaxel were 135, 150, 175, 200 and 225 mg/m^2 in regimen A and 60, 70, 80, 90 and 100 mg/m^2 in regimen B. Toxicity was scored according to the Common Toxicity Criteria of the National Cancer Institute (CTC, version 1.0). Dose-limiting toxicity (DLT) was defined as grade 4 neutropenia lasting $\geqslant 7$ days, grade 3–4 neutropenia with fever $\geqslant 38$ °C for $\geqslant 3$ days, severe infection requiring hospitalisation, platelet count $<25\times10^9$ cells/l and/or $\geqslant$grade 3 non-haematological toxicity (except for nausea and vomiting). The first patient at each dose level was observed for $\geqslant 3$ weeks after initiating therapy. If no excessive toxicity was observed, a minimum of 2 further patients was entered at the same dose level. Dose was escalated in cohorts of 3 patients as long as no DLT was observed; no intrapatient dose escalation was allowed. If 1 out of 3 patients experienced DLT, 3 additional patients were entered at the same dose level. Dose escalation continued if DLT occurred in 1 or 2 out of 6 patients.

Treatment was delayed for 1 week until recovery, for a maximum of 2 weeks, in the following circumstances: WBC $<1000\times10^6$ cells/l and/or platelet count $<50\times10^9$ cells/l on days 8, 15, 36 or 43; WBC $<3000\times10^6$ cells/l and/or platelet count $<100\times10^9$ cells/l on day 29. Cisplatin was withdrawn from the combination regimen when creatinine clearance fell below 45 ml/min, in cases of clinically significant hearing loss and/or disabling neurotoxicity (grade $\geqslant 3$). Paclitaxel was continued according to the schedule of induction chemotherapy, except in cases of $\geqslant$grade 3 neurotoxicity, where continuation of paclitaxel treatment with a 20% dose reduction was optional.

2.3. Sample collection and drug analysis

Blood sampling for cisplatin pharmacokinetic analysis was performed on day 1 of the first chemotherapy

course. Heparinised blood samples were drawn from an indwelling cannula at baseline (0), and at 3 and 4 h after the start of the infusion. Determination of unbound and total cisplatin concentrations in the plasma was performed by flameless atomic absorption spectroscopy with Zeeman-background correction (AAS) as previously described in Ref. [11]. The lower limits of quantitation using 500- and 100-μl samples for unbound and total drug, were 40 and 250 ng/ml, respectively, with the percent deviation from nominal values (accuracy) and precision of the assay always being less than 10%.

Platinum DNA adduct levels in peripheral blood leucocytes were also determined as previously described in Ref. [11]. Following DNA isolation from buffy-coat preparations, samples were digested with DNAse and zinc chloride and injected into the furnace using a 4-times multiple sampling feature of the AAS. The cisplatin DNA-adduct levels were expressed as picogram platinum per microgram DNA (pg Pt/μg DNA).

2.4. Model development and pharmacokinetics

The area under the plasma concentration–time curve (AUC) and the apparent clearance (CL, defined as the dose in mg/m^2 divided by the AUC) of cisplatin were determined from a limited-sampling model (LSM) by stepwise-forward regression analysis using 47 independent data sets [12–14]. All pharmacokinetic parameters are presented as mean values ± standard deviation. The effect of paclitaxel dose on unbound and total cisplatin clearance was evaluated statistically using the Kruskal–Wallis statistic. Probability values (two-sided) of less than 0.05 were regarded as statistically significant.

2.5. Additional chemotherapy

Patients could receive consolidation treatment with paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2 every 3 weeks, or paclitaxel 200 mg/m^2 every 3 weeks. Carboplatin could be used instead of cisplatin in case of compromised renal function and/or clinically significant neurotoxicity or ototoxicity; cyclophosphamide could be substituted for paclitaxel in case of clinically significant neurotoxicity. Optional regimens were paclitaxel/carboplatin or carboplatin/cyclophosphamide 3- or 4-weekly.

2.6. Pretreatment and follow-up studies

Inclusion and exclusion criteria together with all relevant baseline parameters had to be assessed within 2 weeks prior to the initiation of the study treatment. Baseline parameters included complete history, physical, gynaecological and neurological examination, body weight, performance status, vital signs, electrocardiogram, chest X-ray, and abdominal computed tomography (CT) scan. Complete blood count with differential WBC was done at baseline and twice a week during the induction therapy. Physical examination was performed before each administration of chemotherapy along with a measurement of serum sodium, potassium, calcium, magnesium, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, transaminases, lactate dehydrogenase, CA-125, urinalysis and creatinine clearance. Audiometry was not routinely performed. After completion of chemotherapy, patients were followed every 2 months during the first year, every 3 months during the second year and every 4 months thereafter. Follow-up evaluation included physical and gynaecological examination, complete blood count, renal and liver function tests, and CA-125. Abdominal CT scanning was done whenever signs or symptoms of recurrent or progressive disease were noticed.

2.7. Assessment of response, progression-free survival and overall survival

Response evaluation was planned on day 56. Patients who received at least three administrations of weekly cisplatin were considered to be evaluable for response. Response definitions were based on WHO criteria; responses had to be confirmed by two observations with an interval of at least 4 weeks. A senior medical staff member not involved in the conduct of the study reviewed all responses. In case of discrepancy in the response assessment between investigator and independent reviewer, the worst response was taken as the actual response. Disease progression was defined as the appearance of a new lesion and/or $>25\%$ increase of measurable lesions. CA-125 elevation alone was not considered sufficient evidence for disease progression or recurrence.

Patient survival was measured from the first day of the study treatment. The progression-free survival (PFS) and the overall survival (OS) probabilities were calculated using the Kaplan–Meier method, with survival times for survivors censored at 1 April 2001. A non-parametric log-rank test was used for testing the null hypothesis that groups being compared are from the same population as regards survival experience. Statistical analysis was performed using NCSS v5.X (J.L. Hintze, East Kayesville, UT, USA, 1992).

3. Results

3.1. Patient demographics

Patient characteristics are listed in Table 1. A total of 49 patients were entered onto this study in the period between February 1996 and May 1997. 24 of whom 16

Table 1
Patient demographics

		No. of patients (A/B)
Entered		49 (24/25)
Evaluable		46 (22/24)
Age (years)		
Median (range)	53 (23–78)	
WHO performance status		
0		38 (18/20)
1		6 (3/3)
2		2 (1/1)
Tumour histology		
Serous		19 (7/12)
Mucinous		3 (2/1)
Endometrioid		4 (2/2)
Clear cell		1 (0/1)
Adenocarcinoma, not otherwise specified		19 (11/8)
Tumour differentiation grade		
Good		1 (1/0)
Moderate		13 (5/8)
Poor		26 (13/13)
Unknown		6 (3/3)
Disease status		
Chemotherapy-naïve patients ($n=21$)		
FIGO stage		
I		0 (0/0)
II		2 (1/1)
III		15 (4/11)
IV		4 (2/2)
Tumour residue after surgery		
<1 cm		4 (0/4)
1–<5 cm		8 (3/5)
5–10 cm		5 (3/2)
>10 cm		4 (1/3)
Patients with recurrent or platinum-refractory disease ($n=25$)		
Platinum-free interval		
<4 months		8 (4/4)
4–12 months		7 (5/2)
>12 months		10 (6/4)
Target lesions (maximal diameter)		
<5 cm		7 (4/3)
5–10 cm		8 (4/4)
>10 cm		8 (5/3)
Evaluable disease only		2 (2/0)

WHO, World Health Organization; FIGO, International Federation of Gynaecology and Obstetrics.

had recurrent disease, were assigned to treatment regimen A and 25 patients, of whom 10 had recurrent disease, to treatment regimen B. Dose levels of 4-weekly paclitaxel in regimen A were 135 mg/m^2 ($n=4$), 150 mg/m^2 ($n=4$), 175 mg/m^2 ($n=3$), 200 mg/m^2 ($n=7$) and 225 mg/m^2 ($n=6$); dose levels of weekly paclitaxel in regimen B were 60 mg/m^2 ($n=3$), 70 mg/m^2 ($n=4$), 80 mg/m^2 ($n=6$), 90 mg/m^2 ($n=6$), and 100 mg/m^2 ($n=6$).

3 patients were withdrawn from the study within 1 week after the first administration of the study treatment: 1 because of paroxysmal atrial fibrillation and acute cardiac failure, 1 due to rapid development of ileus, and 1 due to patient refusal.

The median age of the 46 fully evaluable patients was 53 years (range 23–78 years), median WHO performance status was 0. All patients had histologically-confirmed adenocarcinoma with primary localisation in one or both ovaries ($n=41$), fallopian tube ($n=2$) or peritoneum (primary extra-ovarian localisation, $n=3$). 44 patients had undergone surgery with the intention of optimal tumour debulking at initial presentation; 2 patients had not had primary surgical treatment because of extensive extraperitoneal metastases.

At study entry, 21 patients were chemotherapy-naïve. Of these, 4 had undergone optimal debulking surgery without measurable residual disease and 17 had

measurable disease at the start of the study treatment (maximal diameter: <5 cm in 8 patients; 5–10 cm in 5 patients; >10 cm in 4 patients).

The 25 patients with recurrent disease had disease progression during or after conventional platinum-based chemotherapy (cisplatin/cyclophosphamide in 15 patients and carboplatin/cyclophosphamide in 10 patients). 2 patients with recurrent disease had evaluable, but no measurable disease (malignant pleuritis and/or peritonitis); the other 23 patients had one or more measurable target lesions.

3.2. Toxicity evaluation

A total of 42 patients completed the study treatment without a dose reduction (regimen A: 20 patients, regimen B: 22 patients). The mean dose intensity of cisplatin was 48.9 mg/m^2/week for regimen A and 50.1 mg/m^2/week for regimen B (intended dose intensity of cisplatin: 52.5 mg/m^2/week). 21 patients received induction chemotherapy without a treatment delay (regimen A: 11 patients, regimen B: 10 patients). 4 of the evaluated patients did not complete induction chemotherapy: 1 due to congestive heart failure after 3 weeks (regimen A), 1 due to grade 3 neurotoxicity at day 29 (regimen A), and 2 because of renal function impairment after 3 and 4 administrations, respectively (regimen B).

Paclitaxel could be escalated to doses used for single agent therapy (i.e. 225 mg/m^2 for the 4-weekly regimen and 100 mg/m^2 for the weekly regimen). Overall, 90 cycles of induction chemotherapy were evaluable for toxicity (43 cycles in regimen A and 47 cycles in regimen B). No toxic deaths were observed.

Haematological toxicity is summarised in Table 2. Anaemia was a common adverse event; blood transfusions were given in cases of symptomatic anaemia. In regimen A, 16 patients received a total of 61 erythrocyte units in 19 out of 43 cycles of induction chemotherapy. In regimen B, 22 patients received a total of 81 erythrocyte units in 30 out of 47 treatment cycles. Grade 3 or 4 neutropenia was observed in 43% of evaluable treatment cycles (44% in regimen A, 43% in regimen B). Neutropenia was generally of brief duration. In only 9 out of 90 cycles (3 in regimen A and 6 in regimen B) neutropenia resulted in a treatment delay $\geqslant 7$ days with a maximum of 14 days (mean 9.9 ± 3.0 days). Febrile neutropenia was rare. One patient (regimen A, paclitaxel dose level 225 mg/m^2) developed grade 4 neutropenia with a fever in the second cycle of chemotherapy, resolving within 2 days of starting empirical antibiotic treatment. Another patient (regimen B, paclitaxel dose level 70 mg/m^2) had 3 days of a fever with grade 3 neutropenia after the fifth administration of the study treatment. Thrombocytopenia was modest. Grade 3 thrombocytopenia was observed in 4/43 cycles of regimen A and in 5/47 cycles of regimen B; 2 patients needed platelet transfusions.

Table 2
Haematological toxicity

Grade[a]	Treatment regimen A					Treatment regimen B				
	0	1	2	3	4	0	1	2	3	4
Anaemia	0	19	24	0	0	0	13	34	0	0
Leucopenia	7	10	12	13	1	5	10	21	11	0
Neutropenia	6	8	10	10	9	1	8	18	16	4
Thrombocytopenia	14	22	3	4	0	26	15	1	5	0

Treatment regimen A = cisplatin 70 mg/m^2 weekly with paclitaxel 4-weekly; treatment regimen B = cisplatin 70 mg/m^2 weekly with paclitaxel weekly. Numbers indicate the number of cycles.

[a] Denotes worst toxicity per cycle (Common Toxicity Criteria, Version 1.0, National Cancer Institute).

Table 3 summarises non-haematological toxicity. Fatigue was frequently observed, especially at the highest paclitaxel dose level in both regimens. Nausea and vomiting were prevalent, but did not result in dose reduction or discontinuation of treatment. Severe allergic reactions were not observed. At completion of the study treatment, neuropathy was absent or mild in most patients. However, cumulative neurotoxicity developed during additional chemotherapy necessitating treatment modification in 13 patients and discontinuation of treatment in 1 patient. Ototoxicity did not result in dose reduction or discontinuation of study treatment. Renal toxicity was manageable in most patients. In 2 out of 46 evaluable patients, cisplatin had to be discontinued after the first cycle of induction chemotherapy because of renal toxicity (both in regimen B). Mean serum creatinine at baseline was 83.4 ± 10.0 μmol/l (range 61–97 μmol/l) in regimen A and 83.3 ± 12.3 μmol/l (range 66–116 μmol/l) in regimen B. The mean of the highest serum creatinine values during the two cycles of induction chemotherapy was 112.5 ± 21.3 μmol/l (range 84–155 μmol/l) for regimen A and 125.2 (range 82–198 μmol/l) for regimen B ($P=0.13$ for comparison of regimen A versus regimen B, Student's t-test). Renal dysfunction was partially reversible: within 1 month after study treatment mean serum creatinine decreased to 102.1 ± 16.7 μmol/l (range 75–140 μmol/l) and 111.5 ± 27.8 μmol/l (range 82–198 μmol/l), respectively. Hypomagnesaemia was common, but did not lead to serious complications and was largely reversible. The baseline serum magnesium of 0.63–1.12 mmol/l (mean 0.84 ± 0.11 mmol/l) for regimen A and 0.68–1.04 mmol/l (mean 0.83 ± 0.08 mmol/l) for regimen B decreased to a nadir of 0.29–0.76 mmol/l (mean 0.60 ± 0.12 mmol/l) and 0.24–0.77 mmol/l (mean 0.51 ± 0.13 mmol/l), respectively ($P=0.0089$, for the comparison of regimen A versus regimen B, Student's t-test). Within 1 month after the induction chemotherapy, the serum magnesium level recovered to 0.44–0.89 mmol/l (mean 0.75 ± 0.10 mmol/l) and 0.58–0.97 mmol/l (mean 0.74 ± 0.10 mmol/l), respectively. Hypomagnesaemia was

Table 3
Non-haematological toxicity

Grade[a]	Treatment regimen A					Treatment regimen B				
	0	1	2	3	4	0	1	2	3	4
Fatigue	16	20	7	0	0	9	26	11	1	0
Nausea	2	20	20	1	0	1	26	13	7	0
Vomiting	8	15	18	1	1	10	14	20	3	0
Diarrhoea	32	9	2	0	0	24	20	3	0	0
Constipation	35	6	2	0	0	28	17	2	0	0
Oral mucositis	40	3	0	0	0	39	8	0	0	0
Taste disturbance	37	6	0	–	–	33	13	1	–	–
Cutaneous	36	6	1	0	0	44	3	0	0	0
Myalgia	22	16	5	0	0	38	9	0	0	0
Arthralgia	37	5	1	0	0	43	4	0	0	0
Neurotoxicity	26	14	2	1	0	31	16	0	0	0
Renal toxicity	24	18	1	0	0	19	23	5	0	0
Hypomagnesaemia	19	19	4	0	1	3	29	11	3	1
Hyponatraemia	23	18	2	0	0	18	23	5	1	0
Hypokalaemia	27	13	2	1	0	32	8	5	2	0
Hypocalcaemia	37	5	0	1	0	31	13	2	1	0

Treatment regimen A = cisplatin 70 mg/m^2 weekly with paclitaxel 4-weekly; 4-treatment regimen B = cisplatin 70 mg/m^2 weekly with paclitaxel weekly. Numbers indicate the number of cycles.

[a] Denotes worst toxicity per cycle (Common Toxicity Criteria, Version 1.0, National Cancer Institute).

more pronounced and developed earlier in regimen B (paclitaxel weekly) than in regimen A (paclitaxel 4-weekly). Hyponatraemia, hypokalaemia and hypocalcaemia were less pronounced than hypomagnesaemia; serious complications due to electrolyte disorders were not encountered in this study.

3.3. Pharmacology

The AUC and apparent clearance of unbound cisplatin was clearly independent of the paclitaxel co-administration (Table 4), similar to published single agent data [15], and not significantly different between the dose levels ($P \geqslant 0.11$). Similarly, the unbound to total drug AUC ratio, as well as total drug clearance were independent of the paclitaxel dose. In order to rule out a potential effect of paclitaxel treatment on cellular cisplatin accumulation, kinetic data were also obtained from all patients following isolation and analysis of peripheral blood cells. The levels of platinum–DNA adducts in leucocytes were independent of the paclitaxel dose (overall mean: 0.51 ± 1.93 pg Pt/μg DNA), although exceptionally high interindividual variability was observed. Interestingly, the mean value is substantially reduced compared with data from 29 patients treated with cisplatin at 70 mg/m^2 in combination with oral etoposide (overall mean: 1.11 ± 0.34 pg Pt/μg DNA) [16]. The mean difference between these groups (-0.60 ± 0.39, 95% confidence limits (CL): -0.98 and -0.36) was significant at $P = 0.002$ (unpaired Student's *t*-test).

3.4. Evaluation of response, progression-free survival and overall survival

After completion of study treatment, 9 chemotherapy-naïve patients had interval debulking surgery. Among the 21 chemotherapy-naïve patients 3 complete responses (CR, all pathologically-confirmed) and 11 partial responses (PR) were observed. 3 patients had stable

Table 4
Pharmacokinetics of unbound and total cisplatin

	Unbound cisplatin		Total cisplatin		
	AUC (μg h/ml)	CL (l/h)	AUC (μg h/ml)	CL (l/h)	U/T ratio (%)
Overall mean	2.64 ± 0.79	50.4 ± 14.9	37.1 ± 7.02	3.42 ± 0.72	7.25 ± 2.16
Range	1.46–4.87	25.7–86.1	19.3–64.0	2.11–6.49	3.72–13.2
CV (%)	29.8	29.5	18.9	21.0	29.9
P value[a]	0.11	0.28	0.99	0.92	0.13

Data are presented as mean values ±Standard Deviation (S.D.) AUC, area under the plasma concentration versus time curve; CL, total plasma clearance; U/T ratio, AUC ratio of unbound and total cisplatin; CV, coefficient of variance.

[a] Kruskal–Wallis statistic with correction for ties for the effect of the paclitaxel dose (60–225 mg/m^2).

disease (SD). The remaining 4 patients had undergone complete surgical debulking at the start of study treatment and were not evaluable for response. Thus, the objective response rate in the chemotherapy-naïve patients was 14/17.

Among the 25 patients receiving study treatment for recurrent disease after first-line chemotherapy 3 CRs, 17 PRs and 5 SDs were obtained. Response rate was 10/10 in patients with a platinum-free interval (PFI) >12 months, 5/7 in patients with PFI of 4–12 months, and 5/8 in patients with PFI <4 months. No patient had disease progression during the study treatment.

43 patients received a median of six cycles (range 1–15 cycles) of additional chemotherapy consisting of cisplatin/paclitaxel ($n=112$), carboplatin/paclitaxel ($n=50$), paclitaxel single agent ($n=35$) and/or carboplatin/cyclophosphamide ($n=48$). 19 chemotherapy-naïve patients had 4–6 cycles, and 24 patients with relapsed disease had 1–15 cycles of additional chemotherapy (in both groups 15 patients received six additional cycles); 2 patients with relapsed disease had more than six additional cycles (1 with 15 cycles of paclitaxel single agent, and 1 with three cycles of cisplatin/paclitaxel followed by four cycles of carboplatin/cyclophosphamide). This resulted in additional responses in several patients: 11 patients with PR after induction chemotherapy as yet obtained CR, and 3 patients with SD as yet obtained objective responses (2 CR, 1 PR). Confirmed maximal responses are summarised in Table 5. Overall, the objective response rate was 16/17 (CR: 11/17, PR: 5/17) for the chemotherapy-naïve patients and 21/25 (CR: 8/25, PR: 13/25) for patients with recurrent disease.

In the entire patient population (49 patients), median PFS was 17 months (range 2.3–55+ months); median OS was 41 months (range 3.0–61+ months). Median PFS was 23 months (range 3–55+ months) in chemotherapy-naïve patients and 11 months (range 2–54+ months) in the patients with recurrent disease; median OS was 48 (range 4–61+ months) and 24 months (range 6–61+ months), respectively. There was no difference in PFS and OS between the patients receiving paclitaxel either 4-weekly or weekly.

4. Discussion

The combination of surgical treatment and chemotherapy with paclitaxel and platinum (either cisplatin or carboplatin) at 3-weekly intervals is considered the 'standard of care' for patients with advanced ovarian cancer [2]. The optimal duration and dose intensity of chemotherapy is unknown, especially with regard to paclitaxel and paclitaxel/platinum combination regimens [17,18]. Several reports have suggested that increasing the dose intensity of cisplatin and/or paclitaxel may result in a better patient outcome [19–23]. However, dose-intensified treatment with paclitaxel and cisplatin has the disadvantage of increased toxicity, which counterbalances possible increases in response rates and PFS [17,18]. Of note, most studies on dose-intensified chemotherapy have focused on increasing the dose without changing the dose interval. An alternative method of increasing dose intensity is by shortening of the treatment interval [24]. In a previous study [10] with cisplatin 70 mg/m^2 weekly for six cycles in combination with prolonged oral administration of etoposide, we have established that weekly platinum chemotherapy is feasible in patients with epithelial ovarian cancer who had failed on, or relapsed after platinum-based combination chemotherapy, yielding an overall objective response rate of 78% in 68 evaluable patients (38–93%, depending on the PFI).

The present study was designed to explore the concept of dose-dense administration of the combination of cisplatin and paclitaxel in patients with advanced ovarian cancer. Cisplatin treatment was intended to be at a dose of 70 mg/m^2 weekly for six administrations with a 1-week break between the third and fourth administrations, resulting in a scheduled cisplatin dose intensity of 52.5 mg/m^2/week. Paclitaxel was administered in escalating doses either 4-weekly (two administrations, 135–150–175–200–225 mg/m^2) or weekly (six administrations, 60–70–80–90–100 mg/m^2), without the use of haematopoietic growth factors. In both regimens of paclitaxel administration, a high cisplatin dose intensity could be reached: 48.9 and 50.1 mg/m^2/week, respectively (corresponding to 93.1 and 95.4% of the

Table 5
Best overall responses

Chemotherapy-naïve ($n=21$)		Recurrent disease ($n=25$)		
		PFI >12 m ($n=10$)	PFI 4–12 m ($n=7$)	PFI <4 m ($n=8$)
CR	11/21	5/10	3/7	0/8
PR	5/21	5/10	3/7	5/8
SD	1/21	0/10	1/7	3/8
PD	0/21	0/10	0/7	0/8
NED	4/21	0/10	0/7	0/8

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NED, no evidence of disease; *n*, number of patients; m, months; PFI, platinum-free interval.

intended dose intensity). Paclitaxel could be escalated to dose levels also used in single-agent treatments; the highest dose intensity was reached with the paclitaxel weekly regimen. Therefore, for further clinical investigations with dose-dense paclitaxel/cisplatin combination chemotherapy, we favour the weekly regimen of paclitaxel 90 mg/m^2 with cisplatin 70 mg/m^2 resulting in dose intensities of 67.5 mg/m^2/week for paclitaxel and 52.5 mg/m^2/week for cisplatin. In terms of dose intensity, this compares favourably with the standard 3-weekly regimen with dose intensities of 58 mg/m^2/week for paclitaxel and 25 mg/m^2/week for cisplatin.

Haematological toxicity was manageable. Grade 4 neutropenia occurred in 14% of the treatment cycles (21% in the paclitaxel 4-weekly and 9% in the paclitaxel weekly regimen). Grade 3 neutropenia was observed in 29% of treatment cycles (23% in the paclitaxel 4-weekly and 34% in the paclitaxel weekly regimen). Only 2 patients had to be admitted to the hospital because of fever during grade 3 or 4 neutropenia. Thrombocytopenia grade 4 was not observed in this study; grade 3 occurred in 10% of treatment cycles (9% in the paclitaxel 4-weekly and 11% in the paclitaxel weekly regimen). Anaemia was frequently encountered in this study, and 38 out of 46 patients (=83%) had to be supported with erythrocyte transfusions, mainly during the second cycle of study treatment. However, erythropoietin was not used in this study, and a significant reduction of the need for erythrocyte transfusions is to be expected when erythropoietin is co-administered.

Non-haematological toxicity was acceptable. Neurotoxicity was absent or mild in the majority of patients. However, cumulative toxicity necessitated modification of consolidation chemotherapy in 13 patients and discontinuation of treatment in 1 patient (out of 44 patients receiving consolidation chemotherapy). This is in accordance with a prospective study that found cisplatin-induced neuropathy to be related to the cumulative dose, but not to the dose intensity of cisplatin [25]. The incidence of myalgia differed between regimens A and B (grade 1: 37% versus 19%, grade 2: 12% versus 0% of the treatment cycles); this could be explained by the higher paclitaxel dose in the 4-weekly compared with the weekly paclitaxel treatment regimen. Renal toxicity was modest and partially reversible after the completion of study treatment; in only 2 out of 46 patients did the creatinine clearance fall below 45 ml/min during the induction treatment necessitating the discontinuation of cisplatin treatment. The administration of cisplatin in a solution with hypertonic saline (NaCl 3% w/v) may have contributed to the alleviation of the nephrotoxic side-effects allowing this dose-dense administration of cisplatin. Animal studies support the hypothesis that an excess of chloride ions during cisplatin infusion can lead to optimal renal excretion of cisplatin with reduced nephrotoxicity [26]. In addition to a possible protective role toward renal toxicity, the hypertonic saline vehicle may also ameliorate cisplatin-induced neuropathy. However, appropriate randomised clinical studies evaluating the role of hypertonic saline in reducing adverse effects of cisplatin have not been done. Hypomagnesaemia was more pronounced during the paclitaxel weekly regimen, which suggests that concomitant administration of paclitaxel enhances the renal tubular toxicity of cisplatin. This was also found in a small retrospective study [27].

In the present study, no pharmacokinetic interaction was found between paclitaxel and cisplatin. Plasma clearance and AUC of total and unbound platinum were not influenced by the paclitaxel dose. Furthermore, the pharmacokinetic parameters did not differ from data when cisplatin is used as a single agent [15]. In contrast to this, platinum–DNA adduct formation in peripheral blood leucocytes was reduced more than 2-fold in the paclitaxel/cisplatin combination chemotherapy compared with cisplatin given as a single agent or cisplatin/etoposide combination treatment [16]. However, no dose–effect relationship could be found between the paclitaxel dose and level of platinum–DNA adducts in the leucocytes, although this could be explained by the exceptionally high interindividual variability in DNA-adduct formation. *In vitro* incubation studies have demonstrated a decrease of intracellular cisplatin accumulation in peripheral blood and bone marrow cells, but not in tumour cell lines, under the influence of the paclitaxel vehicle Cremophor EL [28]. This pharmacodynamic interaction may contribute to the reduced myelotoxicity of the paclitaxel/cisplatin sequence without affecting antitumour activity.

The response rate of dose-dense cisplatin/paclitaxel induction chemotherapy was high, and improved during additional, 3-weekly administered, chemotherapy. The overall response rate was 94% in 17 evaluable patients with previously untreated disease and 84% in 25 evaluable patients with recurrent disease (including 8 patients with a PFI <4 months). This compares favourably to the data using other second-line chemotherapy regimens with response rates of 32–48% [5–7,19,22]. Furthermore, despite important adverse prognostic factors (residual tumour $\geqslant 5$ cm in 25 out of 46 patients, suboptimal disease in 17 out of 21 patients with primary ovarian cancer, PFI $\leqslant 12$ months in 15 out of 25 patients with recurrent ovarian cancer (PFI <4 months in 8 of these patients)), the survival outcome was relatively good if compared with historical data [3,4,6–9,29]. Median PFS was 23 months (range 3–55+ months) in the 21 chemotherapy-naïve patients and 11 months (range 2–54+ months) in the 25 patients with recurrent or platinum-refractory disease; median OS was 48 months (range 4–61+ months) and 24 months (range 6–61+ months), respectively. Although survival was not a primary endpoint of this study, the favourable response

and survival rates suggest that dose-dense platinum/paclitaxel induction chemotherapy followed by paclitaxel and/or platinum-based consolidation treatment deserves further evaluation. We are currently testing this concept in a randomised clinical trial that compares induction chemotherapy (paclitaxel 90 mg/m^2 and cisplatin 70 mg/m^2 at days 1, 8, 15, 29, 36 and 43) followed by consolidation treatment (three courses of paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2 3-weekly) with standard therapy (six courses of paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2 3-weekly).

In conclusion, dose-dense paclitaxel/cisplatin induction treatment followed by consolidation chemotherapy yields excellent response rates with manageable toxicity in patients with advanced ovarian cancer, even in patients with recurrent or platinum-refractory disease.

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