Cisplatin Scheduling and Dosing Aspects

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Klinische en farmacologische aspecten van behandeling met cisplatine

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Ter nagedachtenis aan mijn moeder

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CHAPTER 1

Introduction to the thesis

In 1965, during experiments on the effects of electric fields on cell growth and division, Rosenberg and co-workers found that an electric current delivered between platinum electrodes inhibited the proliferation of Escherichia coli bacteria [1]. This inhibitory effect was found to be related to the formation of inorganic platinum complexes. Additional research showed that the *cis* isomer of dichlorodiammineplatinum II (cisplatin) is an active inhibitor of cell division, whereas the *trans* isomer had no effect on cell growth processes [2]. The antiproliferative activity of cisplatin has been ascribed predominantly to the binding of cisplatin to the N-7 position of adenine and guanine resulting in DNA-platinum adducts with formation of intrastrand and interstrand cross-links [3].

Cisplatin was introduced into the clinic in the early 1970s, and led to considerable improvement in survival of patients with germ cell and ovarian cancer. In addition, cisplatin demonstrated notable activity against epithelial cancers of the lung, head and neck, esophagus, urine bladder, uterine cervix and endometrium [3]. Unfortunately, non-hematological toxicity associated with cisplatin administration was substantial, renal failure (acute tubular necrosis) being the main dose-limiting side effect [4]. Cisplatin administration schedules with hyperhydration greatly improved treatment tolerability, while administration of cisplatin in hypertonic saline vehicle probably had additional renal protective effects [5, 6]. Severe nausea and vomiting (almost universal at cisplatin doses > 50 mg/m^2) became manageable with the introduction of $5HT_3$ antagonists, especially in combination with dexamethasone [7]. Protective measures against gastrointestinal and renal toxicity enabled treatment with larger individual and cumulative doses of cisplatin resulting in more common and sometimes dose-limiting neurotoxicity and ototoxicity [8-10].

With improved supportive care measures, weekly treatment with cisplatin at doses of 70-80 mg/m^2 became feasible [11]. The rationale for weekly administration of high-dose cisplatin was based on the tumor biological principle that frequent administration of chemotherapy at a high dose may result in more effective killing of cancer cells and probably reduces the risk of developing chemotherapy resistance. Furthermore, by shortening the treatment interval, tumor cells have less time for regrowth between treatment courses.

Based on these principles, a phase I/II trial of cisplatin 70 mg/m^2 weekly in combination with escalating doses of paclitaxel either weekly or 4-weekly was carried out in 49 patients with advanced stage ovarian cancer. Primary endpoints in this study were toxicity and antitumor response whereas the pharmacological interaction between paclitaxel and cisplatin was also a subject of interest. Long-term follow-up of this cohort of patients enabled an analysis on progression-free survival and overall survival. The results from this study are presented in chapter 2. In order to investigate the feasibility of weekly high-dose cisplatin treatment on a larger scale, a retrospective analysis was performed in 400 patients, including a thorough assessment of prognostic indicators for toxicity (chapter 3).

Besides studies with focus on the pharmacodynamic aspects of weekly high-dose cisplatin treatment, we opted to include also studies on cisplatin pharmacokinetics. During and shortly after intravenous administration of cisplatin, rapid renal excretion of unbound cisplatin takes place at a clearance rate higher than the glomerular filtration rate, which

was attributed to active renal tubular secretion of cisplatin [12]. However, the cumulative urinary platinum excretion at 24 hours after administration of cisplatin is no more than approximately 25% of the administered platinum dose [13]. This may be explained by progressive, strong and partially irreversible binding to plasma proteins (mainly albumin), whereas binding to cellular proteins and nucleic acids also takes place [14]. Protein binding and cellular toxicity (especially renal tubular toxicity) are influenced by the equilibrium between chlorinated and hydrated platinum species, the hydrated platinum compounds being far more reactive [15-17]. The reduced renal toxicity following administration of cisplatin in hypertonic saline was ascribed to forcing this equilibrium into the direction of the less toxic chlorinated platinum species.

Apart from dose- and schedule dependent influences on pharmacokinetics, toxicity and antitumor efficacy, patient-related factors are of major importance. As for most other anticancer agents, the administered dose of cisplatin is individualized according to a patient's body-surface area (BSA). However, for the majority of anticancer agents clearance is poorly correlated to body-size measures. Hence, the routine use of BSA as the only independent variable considered in drug dosing is questionable [18, 19]. The relation between BSA and clearance of unbound cisplatin has been investigated using pharmacokinetic data of 268 adult cancer patients who were being treated in several prospective studies with cisplatin monotherapy or cisplatin-based combination therapy (chapter 4). In order to further evaluate the impact of (other) patient-related variables on unbound cisplatin clearance, a population pharmacokinetic model incorporating body-size measures (height, weight, BSA) and other patient covariates (age, sex, hematocrit, total protein, albumin, creatinine and creatinine clearance) was developed, as described in chapter 5.

In chapter 6, two commonly applied cisplatin administration schedules using different volumes of hypertonic saline vehicle (250 ml versus 85 ml NaCl 3%) have been compared with regard to plasma pharmacokinetics (10 patients) and urinary platinum excretion (6 patients). This intrapatient pharmacokinetic crossover study also includes an interesting analysis on the relation between plasma chloride concentrations and cisplatin pharmacokinetics.

Finally, implications for the scheduling of cisplatin in clinical practice are discussed, along with recommendations for future studies.

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CHAPTER 2

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/m2 (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.

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 relieve 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 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 most feasible for further study.

PATIENTS AND METHODS

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 ≤ 2, peripheral neuropathy ≤ grade 1, white blood cell count (WBC) ≥ 3000 x 10^6 cells/l, absolute neutrophil count (ANC) ≥ 1500 x 10^6 cells/l, platelet count ≥ 100 x 10^9 cells/l, total bilirubin ≤ 1.25 x upper limit of normal, serum transaminases ≤ 2 x (in case of liver metastases ≤ 3 x) the upper limit of normal, serum creatinine ≤ 120 µmol/l (or creatinine clearance ≥ 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.

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 ≥ 7 days, grade 3-4 neutropenia with fever ≥ 38° Celsius for ≥ 3 days, severe infection requiring hospitalisation, platelet count < 25 x 10^9 cells/l and/or ≥ grade 3 non-haematological toxicity (except for nausea and vomiting). The first patient at each dose level was observed for ≥ 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 x 10^6 cells/l and/or platelet count < 50 x 10^9 cells/l on days 8, 15, 36 or 43; WBC < 3000 x 10^6 cells/l and/or platelet count < 100 x 10^9 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 ≥ 3). Paclitaxel was continued according to the schedule of induction chemotherapy, except in cases of ≥ grade 3 neurotoxicity, where continuation of paclitaxel treatment with a 20% dose reduction was optional.

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 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).

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.

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.

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.

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 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).

RESULTS

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. Twenty-four, of whom 16 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).

Three 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). Forty-four 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.

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-naive 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

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). Two 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.

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). Twenty-one patients received induction chemotherapy without a treatment delay (regimen A: 11 patients, regimen B: 10 patients). Four of the evaluated patients did not complete induction chemotherapy: 1 due to congestive heart failure after 3 weeks, 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 ≥ 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 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 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

Table 2: Haematological toxicity

Grade*	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 treatment cycles.
*Denotes worst toxicity per cycle (Common Toxicity Criteria, Version 1.0, National Cancer Institute).

Table 3: Non-haematological toxicity

	Treatment regimen A					Treatment regimen B				
Grade*	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
Diarrhea	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.
Treatment regimen B = cisplatin 70 mg/m^2 weekly with paclitaxel weekly.
Numbers indicate the number of treatment cycles.
*Denotes worst toxicity per cycle (Common Toxicity Criteria, Version 1.0, National Cancer Institute).

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 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 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.

Pharmacology

The AUC and apparent clearance of unbound cisplatin was clearly independent of the paclitaxel coadministration (Table 4), similar to published single agent data [15], and not significantly different between the dose levels ($P \geq 0.11$). 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).

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*	0.11	0.28	0.99	0.92	0.13

Data are presented as mean values ± standard deviation.
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.
*Kruskal-Wallis statistic with correction for ties for the effect of paclitaxel dose (60-225 mg/m^2).

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.

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. Three patients had stable 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 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.

Forty-three 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). Nineteen 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 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 2-55+ months); median OS was 41 months (range 3-61+ 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 3-61+ months), respectively. There was no difference in PFS and OS between the patients receiving paclitaxel either 4-weekly or weekly.

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/m²/week. Paclitaxel was administered in escalating doses either 4-weekly (two administrations, 135-150-175-200-225 mg/m²) or weekly (six administrations, 60-70-80-90-100 mg/m²), 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/m²/week, respectively (corresponding with 93.1% and 95.4% of the 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/m² with cisplatin 70 mg/m² resulting in dose intensities of 67.5 mg/m²/week for paclitaxel and 52.5 mg/m²/week for cisplatin. In terms of dose intensity, this compares favourably to the standard 3-weekly regimen with dose intensities of 58 mg/m²/week for paclitaxel and 25 mg/m²/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 coadministered.

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 ≥ 5 cm in 25 out of 46 patients, suboptimal disease in 17 out of 21 patients with primary ovarian cancer, PFI ≤ 12 months in 15 out of 25 patients with recurrent ovarian cancer (PFI < 4 months in 8 of these patients)), 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 3-61+ 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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CHAPTER 3

Weekly high-dose cisplatin is a feasible treatment option: analysis on prognostic factors for toxicity in 400 patients

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ABSTRACT

In the present study we describe the toxicity of weekly high-dose (70-85 mg/m^2) cisplatin in 400 patients (203 men, 197 women; median age 54 years) with advanced solid tumours treated in the period 1990-2001 who took part in phase I/II trials, investigating the feasibility and efficacy of weekly cisplatin alone, or in combination with paclitaxel or etoposide. Cisplatin was administered in 250 ml NaCl 3% over 3 h, for six intended administrations. The mean number of administrations was 5.3 (range, 1-6 administrations). Reasons not to complete six cycles were disease progression (7.5%), haematological toxicity (9%), nephrotoxicity (7%), ototoxicity (2.5%), neurotoxicity (1%), gastrointestinal toxicity (1%), cardiovascular complications (0.5%) or a combination of reasons including noncompliance and patient's request (5.5%). Logistic regression analysis was used to evaluate baseline parameters for prognostic value regarding toxicity. Leucopenia correlated with etoposide cotreatment, and thrombocytopenia with cisplatin dose and prior (platinum-based) chemotherapy. Risk factors for nephrotoxicity were older age, female gender, smoking, hypoalbuminaemia and paclitaxel coadministration. Neurotoxicity > grade 1 (11% of patients) was associated with prior chemotherapy and paclitaxel coadministration. Symptomatic hearing loss occurred in 15% with anaemia as the predisposing factor. We conclude that weekly high-dose cisplatin administered in hypertonic saline is a feasible treatment regimen.

INTRODUCTION

Cis-diamminedichloroplatinum (cisplatin) is a commonly used cytotoxic agent with a broad spectrum of activity against solid malignant tumours, including germ cell, ovarian, endometrial, cervical, urothelial, head/neck and lung cancer. When cisplatin was first approved for commercial use in 1978, the major toxicities were severe nausea and vomiting and a high incidence of renal dysfunction. Although these adverse effects are still of concern, they can be significantly reduced by the use of $5HT_3$-receptor antagonists and vigorous hydration [1]. Administration of cisplatin in hypertonic saline may further alleviate nephrotoxic side effects [2]. Protective measures against nausea, vomiting and renal dysfunction have created the opportunity to increase the (individual and cumulative) cisplatin dose. With mild to moderate myelosuppression during conventional 3- or 4-weekly therapy, neurotoxicity [3] and ototoxicity [4] have emerged as the remaining major dose-limiting side effects.

The rationale for weekly administration of high-dose cisplatin is based on the tumour biological principle that frequent administration of chemotherapy in a high dose results in more effective killing of cancer cells and potentially reduces the risk of developing chemotherapy resistance. Furthermore, by shortening the treatment interval, tumour cells have less time for regrowth between treatment courses. Weekly administration of cisplatin has extensively been studied at our institution in a range of prospective clinical trials [5-13].

In the present analysis, we have pooled data of 400 patients treated with cisplatin at weekly doses of 70-85 mg/m^2 for an intended number of six administrations, with the goal of describing in detail the toxicity of this weekly regimen and of identifying predisposing factors for the development of side effects, with an emphasis on nephrotoxicity, neurotoxicity and ototoxicity.

PATIENTS AND METHODS

Patient selection

Patients who had been treated with weekly high-dose cisplatin in the period 1990-2001 were analysed. The majority of patients participated in phase I/II clinical trials [5-13]. All study protocols were approved by the Institutional Ethics Board and all participating patients gave written informed consent. According to the inclusion criteria of the trials, patients were required to have locally advanced or metastatic cancer with no better treatment options than weekly cisplatin as a single agent or in combination with either i.v. paclitaxel or oral etoposide. Age had to be ≥ 18 years, WHO performance status 0-2, and life expectancy more than 12 weeks with adequate haematopoietic, renal and hepatic function at study entry. Based on favourable treatment results [10], patients with locally advanced head/neck cancer could be offered treatment with weekly cisplatin induction chemotherapy followed by radiotherapy outside study protocols.

Treatment

Cisplatin was administered at a dose of 70-85 mg/m^2 on days 1, 8, 15, 22, 29 and 36 as a single agent, or at a dose of 70 mg/m^2 on days 1, 8, 15, 29, 36 and 43 in combination with oral etoposide or i.v. paclitaxel. Cisplatin powder was dissolved in 250 ml NaCl 3% and administered by i.v. infusion over 3 h. Patients received prehydration with 1 l normal saline or dextrose-saline and posthydration with 3 l normal saline or dextrose-saline supplemented with KCl (20 mmol/l) and $MgSO_4$ (2 g/l). Antiemetic prophylaxis consisted of a $5HT_3$ antagonist in combination with dexamethasone. Diuretics were not administered routinely.

Dose intensity

Dose reductions were not allowed. Cisplatin single-agent treatment was postponed 1 week for a maximum of 3 weeks if WBC < 2.5 x 10^9/l and/or platelets < 75 x 10^9/l. When used in combination with etoposide, cisplatin administration was postponed in the case of WBC < 2.5 x 10^9/l and/or platelets < 75 x 10^9/l on day 8 or day 36, WBC < 1.5 x 10^9/l and/or platelets < 50 x 10^9/l on day 15 or day 43, and WBC < 3.0 x 10^9/l and/or platelets < 100 x 10^9/l on day 29. With the cisplatin/paclitaxel regimen, treatment was postponed if WBC <

1.0 x 10^9/l and/or platelets < 50 x 10^9/l on days 8, 15, 36 or 43, and if on day 29 WBC < 3.0 x 10^9/l and/or platelets < 100 x 10^9/l. Cisplatin was discontinued if creatinine clearance fell below 45 ml/min or in case of neurotoxicity > grade 2.

The planned dose intensity was calculated by dividing the planned total dose of cisplatin (mg/m^2) by the planned duration of treatment given in weeks (i.e. 6 weeks for cisplatin single agent and 7 weeks for cisplatin in combination with etoposide or paclitaxel). The achieved dose intensity was calculated by dividing the total administered dose (mg/m^2) by the actual treatment duration given in weeks. Patients who did not complete treatment due to nontoxicity reasons (e.g. disease progression, noncompliance) were not evaluated for achieved dose intensity.

Data collection and statistical analysis

Pretreatment and follow-up studies have been reported in detail elsewhere [5-13]. Patients' baseline characteristics analysed included age, sex, length, weight, body-surface area (BSA), blood pressure, smoking and drinking habits, amount of weight loss, performance status, tumour type, prior anticancer treatment, planned cisplatin dose and dose intensity, and cytotoxic comedication (etoposide, paclitaxel or none). Physical examination, laboratory tests and assessment of toxicity were performed weekly during treatment. Laboratory tests included haemoglobin, WBC, granulocytes, platelets, albumin, bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), sodium, potassium, calcium, magnesium, creatinine and creatinine clearance measured by 24-h urine collection. In addition, creatinine clearance was estimated using the Cockroft and Gault equation. Toxicity was assessed according to the Common Toxicity Criteria (CTC), version 1.0, National Cancer Institute (NCI), and, for the present analysis, was evaluated after three administrations of weekly cisplatin, after six administrations and 3 months after completion of the weekly cisplatin regimen. Since audiograms were not routinely performed, grade 1 ototoxicity was not reported. Patients who went off treatment before the fifth administration of cisplatin for reasons other than the evaluated toxicity were excluded from analysis of that toxicity, in order to prevent under-reporting of toxicity.

Logistic regression analysis was used in order to test baseline parameters for their prognostic value regarding toxicity. Patients with neurological symptoms or hearing impairment at baseline were excluded from logistic regression analysis for neurotoxicity and ototoxicity, respectively. In order to eliminate the influence of baseline serum creatinine and creatinine clearance on renal toxicity assessment, renal toxicity was defined as a ≥ 25% decline in the estimated creatinine clearance from baseline. After univariate analysis, all baseline parameters were presented to the multivariate model that used a stepwise procedure starting with an empty model and putting the most significant factor at that time into the model. This process was repeated until the *P*-value of the factor involved exceeded 0.025. This level of statistical significance was chosen to reduce the risk of finding purely coincidental associations in view of the large amount of factors

analysed. *P*-values were calculated using the Wald test. For each parameter remaining in the multivariate model, an odds ratio (OR) with 95% confidence interval (CI) for the development of toxicity was calculated.

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. A total of 400 patients (203 males, 197 females) who had been receiving a total of 2116 weekly cisplatin administrations were included in the study. Predominant tumour types were head and neck cancer (39%) and ovarian cancer (27%). Of the 92 patients with prior chemotherapy, 88 patients had recurrent ovarian cancer after one or more platinum-based regimens (cisplatin pretreatment in 40 patients).

The planned cisplatin dose was 70 mg/m^2 for 323 patients (81%) and 80 mg/m^2 for 70 patients (18%). Five patients received 75 mg/m^2, and 2 received 85 mg/m^2. Cisplatin was administered as a single agent to 143 patients (36%); 196 patients (49%) received cisplatin in combination with oral etoposide and 61 (15%) with i.v. paclitaxel. A total of 263 patients (66%) received six cisplatin administrations: 151 without any delay (38%), 64 with 1 week delay (16%), 39 with 2 weeks delay (10%), 7 with 3 weeks delay (2%), and 2 with 4 weeks delay (0.5%). From the patients that received four (n = 30) or five (n = 59) administrations of cisplatin, 55 had no treatment delay (14%), 18 had 1 week delay (4.5%), 10 had 2 weeks delay (2.5%), and 6 had 3 weeks delay (1.5%); from the patients that received one (n = 8), two (n = 5) or three (n = 35) cisplatin administrations, 46 had no delay (11%) and 2 had a 1-week treatment delay (0.5%). The mean number of cisplatin administrations was 5.3, with a median total cisplatin dose 420 mg/m^2 (range, 70-480 mg/m^2; mean, 379 ± 86 mg/m^2). The mean duration of treatment was 6.5 ± 1.9 weeks (range, 1-11 weeks; median, 7 weeks). The median achieved dose intensity was 60 mg/m^2/week (range, 10-80 mg/m^2/week; mean, 55.7 ± 11.6 mg/m^2/week).

Toxicity incidences (scored as the worst CTC grade) are shown in Table 2. Nausea and vomiting were prevalent but did not result in dose reduction or cessation of treatment. Reasons not to complete treatment were disease progression (30 patients, 7.5%), haematological toxicity (37 patients, 9%), renal toxicity (29 patients, 7%), ototoxicity (10 patients, 2.5%), neurotoxicity (4 patients, 1%), gastrointestinal toxicity (3 patients, 1%), cardiovascular complications (2 patients, 0.5%), or combinations of reasons including noncompliance and patient's request (22 patients, 5.5%). In total, 12 patients (3%) died within 30 days after the last administration of weekly cisplatin; 9 of them had rapidly progressive disease.

Table 1: Patient characteristics (n = 400)

		No. of patients	(%)
Sex			
Male		203	51
Female		197	49
Age (years)			
Median	54		
Range	19-79		
WHO performance status			
0		157	39
1		206	51
2		34	9
Unknown		3	1
Tumour type			
Head and neck cancer		155	39
Ovarian cancer		108	27
CUP		47	12
NSCLC		36	9
Mesothelioma		24	6
Glioma		18	4
Miscellaneous		12	3
Prior chemotherapy			
None		308	77
Platinum-based		88	22
Non-platinum-based		4	1

WHO, World Health Organization; CUP, carcinoma with unknown primary; NSCLC, non-small-cell lung cancer.

Table 2: Toxicity (%) of weekly cisplatin in 400 patients (worst toxicity per patient)

CTC GRADE*	0	1	2	3	4
Anaemia	1	34	44	20	1
Leucopenia	10	18	35	30	7
Neutropenia	10	9	25	32	24
Thrombocytopenia	27	34	17	14	8
Nausea	18	44	30	8	0
Vomiting	36	30	27	6	1
Nephrotoxicity	59	32	8	1	0
Hypomagnesaemia	33	52	9	5	1
Hyponatraemia	55	23	18	3	1
Hypokalaemia	81	13	5	1	0
Hypocalcaemia	53	40	5	1	1
Neurotoxicity	53	36	8	3	0
Ototoxicity#	58	-	27	14	1

*Common Toxicity Criteria, Version 1.0, National Cancer Institute.
#Audiometry was not routinely performed: grade 0 ototoxicity should be interpreted as grade 0 or 1.

Haematological toxicity

In 37 patients (9%), weekly cisplatin treatment was discontinued because of haematological toxicity, in the majority of them (21 patients) only after the fifth administration. Anaemia was a common adverse event. During the evaluation period 202 patients (51%) received one or more transfusions. The median number of erythrocyte units transfused was two (range, 0-17). Grade 3-4 leucopenia was common, and associated with etoposide cotreatment (OR = 2.2, P = 0.007). Although frequently observed, grade 4 neutropenia was generally brief (< 7 days in 74%; < 14 days in 94%) and uncomplicated. Febrile neutropenia occurred in only 1.5% of patients. Grade 3-4 thrombocytopenia was observed in 22% of patients who received at least three administrations of weekly cisplatin; 19 patients (5%) received platelet transfusions. Thrombocytopenia was associated with prior chemotherapy (OR = 3.2, P = 0.006) and cisplatin dose (80 mg/m^2 versus 70 mg/m^2: OR = 2.9, P = 0.009). Paclitaxel coadministration was not associated with enhanced haematological toxicity (OR = 0.39, P = 0.1 for anaemia; OR = 1.9, P = 0.08 for leucopenia; OR = 0.53, P = 0.2 for neutropenia; OR = 0.55, P = 0.3 for thrombocytopenia).

Nephrotoxicity

At baseline, serum creatinine (mean ± standard deviation) was 84 ± 14 µmol/l with an estimated creatinine clearance of 83 ± 22 ml/min. After three and six administrations of weekly cisplatin, the serum creatinine was 93 ± 40 and 102 ± 29 µmol/l respectively with an estimated creatinine clearance of 77 ± 23 and 69 ± 23 ml/min respectively. A ≥ 25% reduction in creatinine clearance was observed in 116 patients (29%). In 164 patients (41%) the serum creatinine rose above the upper limit of normal (grade 1, 127 patients (32%); grade 2, 35 patients (9%); grade 3, two patients (0.5%)). Electrolyte disorders were frequently observed. Mean ± standard deviation serum concentrations of magnesium, calcium, sodium and potassium declined from respectively 0.81 ± 0.09 mmol/l (range, 0.51-1.33 mmol/l), 2.39 ± 0.14 mmol/l (range, 1.92-3.03 mmol/l), 139 ± 3.7 mmol/l (range, 128-149 mmol/l) and 4.2 ± 0.41 mmol/l (range, 2.8-5.5 mmol/l) at baseline to 0.70 ± 0.13 mmol/l (range, 0.22-1.62 mmol/l), 2.26 ± 0.15 mmol/l (range, 1.59-2.69 mmol/l), 135 ± 4.3 mmol/l (range, 117-146 mmol/l) and 4.0 ± 0.50 mmol/l (range, 2.5-5.2 mmol/l) after three administrations, and 0.62 ± 0.14 mmol/l (range, 0.23-1.16 mmol/l), 2.24 ± 0.16 mmol/l (range, 1.53-2.69 mmol/l), 135 ± 4.1 mmol/l (range, 122-146 mmol/l) and 4.0 ± 0.56 mmol/l (range, 2.2-5.6 mmol/l) after six administrations of weekly cisplatin.

Results of the logistic regression analysis for nephrotoxicity are shown in Table 3. In the univariate analysis, age, female sex, prior cisplatin treatment, paclitaxel cotreatment and hypoalbuminaemia were associated with nephrotoxicity (defined as ≥ 25% decline of the estimated creatinine clearance at any time during the evaluation period). After adjustment for prior chemotherapy and additional chemotherapeutical agents, age and hypoalbuminaemia remained significant whereas smoking and elevated serum alkaline

Table 3: Logistic regression analysis for nephrotoxicity[a]

	Unadjusted		Adjusted[b]	
Baseline parameter	**Odds ratio (CI)**	***P*-value**	**Odds ratio (CI)**	***P*-value**
Univariate analysis				
Age (year^{-1})	1.03 (1.00-1.05)	0.027	1.03 (1.00-1.05)	0.028
Sex (female)	1.71 (1.09-2.70)	0.021	1.46 (0.84-2.57)	0.183
BSA (m^{-2})	0.79 (0.24-2.61)	0.696	0.97 (0.28-3.41)	0.966
Performance status > 1	1.01 (0.41-2.45)	0.987	0.88 (0.35-2.23)	0.794
Tumour type (ovarian cancer)	1.54 (0.89-2.66)	0.124	0.63 (0.17-2.29)	0.478
Prior carboplatin treatment	0.85 (0.42-1.71)	0.656		
Prior cisplatin treatment	2.16 (1.06-4.39)	0.035		
Cisplatin dose ≥ 80 mg/m^2	1.16 (0.65-2.09)	0.610	2.07 (0.99-4.30)	0.052
Paclitaxel cotreatment	3.46 (1.80-6.66)	<0.001		
Etoposide cotreatment	1.11 (0.66-1.88)	0.687		
Weight loss > 5%	0.99 (0.61-1.62)	0.978	1.18 (0.70-1.99)	0.530
Smoking	1.21 (0.75-1.97)	0.436	1.80 (1.01-3.22)	0.046
Alcohol intake > 2 units/day	1.25 (0.76-2.03)	0.370	1.77 (0.96-3.23)	0.066
Systolic BP > 150 mmHg	1.44 (0.82-2.52)	0.206	1.30 (0.72-2.34)	0.387
Diastolic BP > 90 mmHg	0.68 (0.34-1.38)	0.287	0.70 (0.34-1.46)	0.347
Creatinine clearance < 70 ml/min	1.24 (0.77-2.01)	0.378	1.04 (0.62-1.74)	0.876
Hyponatraemia (< 135 mmol/l)	0.99 (0.50-1.96)	0.968	1.17 (0.58-2.39)	0.657
Hypokalaemia (< 4.0 mmol/l)	1.36 (0.79-2.33)	0.271	1.33 (0.76-2.33)	0.319
Hypocalcaemia (< 2.2 mmol/l)	0.95 (0.39-2.29)	0.907	0.95 (0.38-2.36)	0.911
Hypomagnesaemia (< 0.7 mmol/l)	2.15 (0.80-5.79)	0.129	2.31 (0.82-6.51)	0.113
Anaemia (haemoglobin < normal)	0.95 (0.61-1.49)	0.826	1.11 (0.69-1.79)	0.665
Hypoalbuminaemia (< 35 g/l)	3.13 (1.36-7.22)	0.007	3.22 (1.36-7.61)	0.008
Alkaline phosphatase > normal	1.85 (0.93-3.65)	0.078	2.42 (1.17-4.97)	0.016
AST > normal	1.61 (0.65-3.99)	0.308	1.47 (0.57-3.83)	0.428
ALT > normal	1.83 (0.91-3.67)	0.091	1.72 (0.83-3.58)	0.145
LDH > normal	1.10 (0.64-1.89)	0.734	1.19 (0.66-2.16)	0.568

Independent risk factor	**Odds ratio (CI)**	***P*-value**
Multivariate analysis		
Paclitaxel cotreatment	4.01 (1.83-8.77)	0.001
Smoking	2.50 (1.39-4.51)	0.002
Hypoalbuminaemia	3.49 (1.44-8.45)	0.006
Age (year^{-1})	1.03 (1.01-1.06)	0.007
Female gender	1.99 (1.09-3.63)	0.025

CI, 95% confidence interval; BSA, body-surface area; BP, blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.
[a]Nephrotoxicity defined as ≥ 25% decline in estimated creatine clearance (Cockroft-Gault).
[b]Adjusted for prior chemotherapy and cytotoxic cotreatment (paclitaxel, etoposide).

phosphatase concentrations were introduced as additional risk factors. The multivariate analysis selected age, female gender, smoking, paclitaxel coadministration and hypoalbuminaemia as independent risk factors. Paclitaxel cotreatment (OR = 4.0, P = 0.001), hypoalbuminaemia (OR = 3.5, P = 0.006) and smoking (OR = 2.5, P = 0.002) were strong predisposing factors for renal toxicity in the multivariate model. There was a gradual increase in renal toxicity with increasing age at an OR of 1.03/year (P = 0.007). Patients younger than 48 years had a 26% risk for renal toxicity, which increased to 35% for patients aged 48-62 years and 41% for patients > 62 years. Compared with men, women had a two-fold risk of renal toxicity (OR = 2.0, P = 0.02).

Neurotoxicity

Clinical data on neurotoxicity (according to CTC criteria) were fully available for the period of weekly cisplatin treatment, but were missing in 71 of our patients (18%) at 2-4 months post-treatment. Furthermore, it is noteworthy that 43 ovarian cancer patients treated with weekly cisplatin in combination with paclitaxel (11% of the study population) received additional 3-weekly treatment with cisplatin and/or paclitaxel immediately following the weekly regimen. Neurotoxicity (mostly peripheral sensory polyneuropathy) was observed in 188 patients (47%) and was mild to moderate in most cases: 145 patients (36%) developed grade 1 neurotoxicity, 33 patients grade 2 (8%), 9 patients (2%) grade 3, and 1 patient experienced grade 4 neurotoxicity.

After univariate analysis a large number of baseline parameters were found to be related with the development of grade 2-4 neurotoxicity: female sex, tumour type (ovarian cancer), prior chemotherapy, cisplatin dose, paclitaxel coadministration, nonsmoking and alcohol consumption ≤ 2 units/day (Table 4). After adjustment for prior chemotherapy and cytotoxic cotreatment, none of the (other) risk factors remained significant. After multivariate analysis, prior platinum-based chemotherapy (cisplatin or carboplatin) and coadministration of paclitaxel remained independent prognostic indicators for neurotoxicity. The ORs were 8.3 for paclitaxel coadministration (P = 0.001), 3.9 for pretreatment with cisplatin (P = 0.01), and 3.5 for pretreatment with carboplatin (P = 0.01).

Ototoxicity

Ototoxicity was observed in 168 patients (42%): 110 patients (28%) had CTC grade 2 (reversible tinnitus), 55 (14%) grade 3, and 3 patients (1%) had grade 4 ototoxicity. Table 5 shows the results of the logistic regression analysis for ototoxicity defined as symptomatic hearing loss (grade 3-4). Anaemia was the single baseline parameter associated with ototoxicity (OR = 3.1, P = 0.001).

Table 4: Logistic regression analysis for neurotoxicity[a]

	Unadjusted		Adjusted[b]	
Baseline parameter	**Odds ratio (CI)**	***P*-value**	**Odds ratio (CI)**	***P*-value**
Univariate analysis				
Age (year^{-1})	1.03 (0.99-1.07)	0.129	1.02 (0.98-1.06)	0.286
Sex (female)	4.73 (2.01-11.2)	<0.001	1.53 (0.50-4.65)	0.452
BSA (m^{-2})	0.48 (0.07-3.12)	0.442	0.68 (0.06-7.41)	0.750
Performance status > 1	1.42 (0.40-5.11)	0.589	1.23 (0.29-5.22)	0.780
Tumour type (ovarian cancer)	8.69 (3.19-23.6)	<0.001	4.57 (0.63-33.2)	0.133
Prior carboplatin treatment	4.07 (1.71-9.68)	0.001		
Prior cisplatin treatment	6.48 (2.63-16.0)	<0.001		
Cisplatin dose ≥ 80 mg/m^2	0.13 (0.02-0.96)	0.045	0.37 (0.04-3.38)	0.375
Paclitaxel cotreatment	15.3 (4.89-47.9)	<0.001		
Etoposide cotreatment	2.12 (0.67-6.67)	0.203		
Weight loss > 5%	0.83 (0.39-1.80)	0.643	2.00 (0.79-5.06)	0.144
Smoking	0.23 (0.09-0.60)	0.003	0.46 (0.16-1.34)	0.153
Alcohol intake > 2 units/day	0.27 (0.09-0.79)	0.017	0.42 (0.12-1.43)	0.167
Systolic BP > 150 mmHg	1.72 (0.78-3.79)	0.176	1.32 (0.52-3.34)	0.556
Diastolic BP > 90 mmHg	0.35 (0.08-1.51)	0.160	0.35 (0.07-1.66)	0.186
Creatinine clearance < 70 ml/min	1.72 (0.84-3.53)	0.140	1.07 (0.47-2.45)	0.872
Hyponatraemia (< 135 mmol/l)	0.39 (0.09-1.71)	0.214	0.72 (0.15-3.39)	0.678
Hypokalaemia (< 4.0 mmol/l)	0.63 (0.24-1.69)	0.361	0.56 (0.19-1.69)	0.303
Hypocalcaemia (< 2.2 mmol/l)	1.85 (0.59-5.82)	0.290	2.06 (0.58-7.34)	0.268
Hypomagnesaemia (< 0.7 mmol/l)	0.48 (0.06-3.77)	0.484	0.27 (0.03-2.53)	0.252
Anaemia (haemoglobin < normal)	1.09 (0.54-2.20)	0.801	1.84 (0.80-4.20)	0.149
Hypoalbuminaemia (< 35 g/l)	0.82 (0.18-3.69)	0.800	0.77 (0.15-3.96)	0.754
Alkaline phosphatase > normal	0.43 (0.10-1.89)	0.266	0.89 (0.19-4.23)	0.885
AST > normal	1.53 (0.42-5.52)	0.518	1.27 (0.29-5.53)	0.753
ALT > normal	1.37 (0.50-3.79)	0.543	1.08 (0.34-3.47)	0.892
LDH > normal	1.07 (0.46-2.47)	0.871	1.13 (0.43-2.98)	0.809

Independent risk factor	**Odds ratio (CI)**	***P*-value**
Multivariate analysis		
Paclitaxel cotreatment	8.33 (2.43-28.5)	0.001
Prior cisplatin treatment	3.88 (1.38-10.9)	0.010
Prior carboplatin treatment	3.50 (1.29-9.48)	0.014

CI, 95% confidence interval; BSA, body-surface area; BP, blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.

[a]Neurotoxicity defined as CTC grade 2-4.

[b]Adjusted for prior chemotherapy and cytotoxic cotreatment (paclitaxel, etoposide).

Table 5: Logistic regression analysis for ototoxicity[a]

	Unadjusted		Adjusted[b]	
Baseline parameter	**Odds ratio (CI)**	***P*-value**	**Odds ratio (CI)**	***P*-value**
Univariate analysis				
Age (year^{-1})	0.99 (0.97-1.02)	0.699	0.99 (0.96-1.02)	0.635
Sex (female)	1.18 (0.65-2.13)	0.595	1.06 (0.51-2.23)	0.871
BSA (m^{-2})	0.25 (0.05-1.28)	0.097	0.31 (0.06-1.65)	0.169
Performance status > 1	0.86 (0.24-3.03)	0.815	0.96 (0.27-3.44)	0.945
Tumour type (ovarian cancer)	1.27 (0.63-2.57)	0.501	2.18 (0.43-11.1)	0.347
Prior carboplatin treatment	1.33 (0.60-2.99)	0.484		
Prior cisplatin treatment	0.74 (0.24-2.21)	0.584		
Cisplatin dose ≥ 80 mg/m^2	0.75 (0.32-1.76)	0.506	0.67 (0.25-1.80)	0.430
Paclitaxel cotreatment	1.81 (0.82-4.01)	0.141		
Etoposide cotreatment	0.71 (0.36-1.41)	0.324		
Weight loss > 5%	1.34 (0.72-2.50)	0.354	1.54 (0.79-2.97)	0.203
Smoking	1.30 (0.67-2.53)	0.432	1.48 (0.69-3.16)	0.310
Alcohol intake > 2 units/day	1.30 (0.69-2.44)	0.413	1.25 (0.59-2.67)	0.561
Systolic BP > 150 mmHg	0.65 (0.28-1.51)	0.314	0.66 (0.28-1.60)	0.361
Diastolic BP > 90 mmHg	0.36 (0.11-1.20)	0.096	0.40 (0.12-1.36)	0.141
Creatinine clearance < 70 ml/min	1.26 (0.67-2.38)	0.479	1.21 (0.62-2.33)	0.577
Hyponatraemia (< 135 mmol/l)	0.92 (0.36-2.31)	0.854	1.12 (0.43-2.89)	0.816
Hypokalaemia (< 4.0 mmol/l)	0.81 (0.37-1.76)	0.597	0.85 (0.39-1.87)	0.686
Hypocalcaemia (< 2.2 mmol/l)	0.82 (0.23-2.87)	0.754	0.93 (0.26-3.32)	0.909
Hypomagnesaemia (< 0.7 mmol/l)	1.08 (0.29-3.98)	0.913	0.81 (0.21-3.21)	0.765
Anaemia (haemoglobin < normal)	2.38 (1.25-4.53)	0.008	3.14 (1.57-6.27)	0.001
Hypoalbuminaemia (< 35 g/l)	1.96 (0.74-5.25)	0.178	2.38 (0.85-6.66)	0.099
Alkaline phosphatase > normal	0.61 (0.21-1.79)	0.365	0.77 (0.25-2.35)	0.641
AST > normal	1.34 (0.43-4.18)	0.616	1.36 (0.42-4.35)	0.606
ALT > normal	1.31 (0.54-3.17)	0.551	1.41 (0.56-3.53)	0.466
LDH > normal	1.26 (0.63-2.52)	0.508	1.74 (0.81-3.73)	0.159

Independent risk factor	**Odds ratio (CI)**	***P*-value**
Multivariate analysis		
Anaemia	3.14 (1.57-6.27)	0.001

CI, 95% confidence interval; BSA, body-surface area; BP, blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate ehydrogenase.

[a]Ototoxicity defined as symptomatic hearing loss (CTC grade 3-4).

[b]Adjusted for prior chemotherapy and cytotoxic cotreatment (paclitaxel, etoposide).

DISCUSSION

The present study reports the toxic side effects of weekly high-dose cisplatin chemotherapy in 400 patients with locally advanced and/or metastatic cancer. Given the median number of six administrations of weekly cisplatin, the median total dose of 420 mg/m^2 and the median dose-intensity of 60 mg/m^2/week, it can be concluded that a short intensive weekly cisplatin schedule is a feasible treatment option, even in combination with i.v. paclitaxel or oral etoposide.

Haematological toxicity resulted in treatment discontinuation in only 9% of patients (the majority of them only missing one administration of weekly cisplatin). Anaemia, however, was frequently observed, and 51% of the patients received erythrocyte transfusions. Grade 3-4 neutropenia and thrombocytopenia were present, but generally of brief duration and without serious complications. It is noteworthy that paclitaxel cotreatment (in contrast to etoposide coadministration) did not result in enhanced haematological toxicity; this could be explained by a favourable pharmacological interaction between cisplatin and cremophor EL (the vehicle for i.v. paclitaxel administration). It is already known that the sequence paclitaxel-cisplatin induces less profound neutropenia than the alternate sequence, which was first ascribed to lower paclitaxel clearance rates after cisplatin administration [14]. In other studies, however, no pharmacokinetic interaction between paclitaxel and cisplatin could be found [15], whereas *in vitro* drug accumulation studies have demonstrated significant reduction of intracellular cisplatin concentrations in leucocytes (but not in tumour cells) in the presence of cremophor EL, which was not observed with paclitaxel alone [16]. The infusion of cremophor EL immediately before cisplatin administration ameliorated leucopenia, neutropenia and thrombocytopenia [15], which may be of potential interest for improvement of the therapeutic index of weekly cisplatin treatment.

Renal toxicity was present and necessitated discontinuation of weekly cisplatin treatment in 7% of patients. According to CTC criteria, nephrotoxicity was observed in 42% of patients (serum creatinine above upper limit of normal); the majority of them (32%) experienced mild (grade 1) renal toxicity, whereas 5% of the patients already had elevated serum creatinine concentrations at baseline. The estimated creatinine clearance declined from 83 ± 22 ml/min at baseline to 69 ± 23 ml/min after six administrations of weekly cisplatin. In 116 patients (29%), creatinine clearance decreased 25% or more; the median decrease in creatinine clearance was 16%. This certainly does not exceed the nephrotoxicity reported from conventional 3-weekly cisplatin treatment, and confirms previous observations that haematological, and not renal, toxicity is the major dose-limiting adverse event of weekly high-dose cisplatin chemotherapy [5, 9, 10]. The administration of cisplatin in a solution with hypertonic saline may have alleviated renal toxicity, thus allowing dose-dense cisplatin treatment. In animal models it has been shown that administration of cisplatin in a vehicle of hypertonic saline remarkably reduced nephrotoxicity without loss of antitumour activity [17]. The most likely explanation is that chloride excess results in decreased formation of highly nephrotoxic hydrolysis products

of cisplatin [18-20].

Several baseline parameters were identified as independent prognostic indicators for renal toxicity. The incidence of nephrotoxicity gradually increased with age (OR = 1.03/year). Although increased age was a risk factor for nephrotoxicity, our study also demonstrates that weekly cisplatin treatment is not necessarily contraindicated in elderly patients. Women had a two-fold increased risk for renal toxicity compared with men. The reason for this gender difference is not known. In a previous study [21], we found that unbound cisplatin clearance was 15% higher in men than in women but age had no significant influence on this clearance. Paclitaxel coadministration was strongly related to the development of nephrotoxicity (OR = 4.0, CI = 1.8-8.8). Although the mechanism of this association is not clear, it is in concordance with a report of increased nephrotoxicity with paclitaxel/cisplatin combination as compared to cisplatin single-agent chemotherapy in a small group of patients with gynaecologic cancers [22]. Smoking also was an independent risk factor for cisplatin-induced nephrotoxicity in the present study (OR = 2.5, CI = 1.4-4.5). To our knowledge, this has not been reported in the literature, and the underlying pathophysiological mechanism remains a matter of speculation. It is known, however, that cigarette smoking is associated with oxidative stress [23], which could possibly lead to enhanced formation of nephrotoxic platinum metabolites. Although it cannot be excluded that smoking was associated with nephrotoxicity through coexisting smoking-related cardiovascular disease, other indicators for cardiovascular disease such as hypertension and diminished baseline creatinine clearance were not identified as risk factors for cisplatin-induced nephrotoxicity. Furthermore, there was no association between nephrotoxicity and a history of hypertension, cardiovascular disease or diabetes mellitus in 425 patients treated with conventional cisplatin chemotherapy [24]. Another strong predisposing factor for renal toxicity was hypoalbuminaemia. This has also been described for patients receiving conventional cisplatin treatment [24]. Various studies have demonstrated that cisplatin-induced nephrotoxicity is related to the peak plasma concentration and/or the area under the plasma concentration-time curve of nonprotein bound cisplatin [25-27]. It is postulated that low serum albumin concentrations are associated with increased plasma concentrations of unbound cisplatin, resulting in enhanced renal toxicity. It is noteworthy that cisplatin dose (in the range 70-80 mg/m^2) was not associated with nephrotoxicity and that baseline creatinine clearance did not predict for nephrotoxicity (defined as relative decrease in estimated creatinine clearance), both findings confirming data on conventional cisplatin treatment [28].

Neurotoxicity was found to be acceptable with weekly cisplatin chemotherapy. According to previous studies, neurotoxicity is mainly related to cumulative cisplatin dose, and shortening of the treatment interval does not necessarily lead to worsening of the neurotoxic side effects [29-31]. Neurotoxicity was evaluated during and immediately following the weekly cisplatin regimen. Since cisplatin-induced neuropathy can worsen during the first months after cisplatin treatment [30], it was also assessed 2-4 months after the completion of the weekly cisplatin regimen. The worst toxicity score was used for evaluation of neurotoxicity. Here, several biases were met. First, data on neurotoxicity at

2-4 months were not traceable in 71 patients (18%), which probably led to some underestimation of neurotoxicity. On the other hand, 11% of the total study population received additional paclitaxel and/or cisplatin immediately following the weekly cisplatin regimen with possible overestimation of neurotoxicity. Nevertheless, only 4 patients (1%) did not complete treatment due to neurotoxicity. CTC grade 2-4 neurotoxicity was observed in 11% of the patients.

A large number of baseline parameters were identified as potential risk factors for cisplatin-induced neurotoxicity by univariate logistic regression analysis (Table 4): female sex, ovarian cancer, prior platinum-based chemotherapy, individual cisplatin dose, nonsmoking and alcohol consumption < 3 units daily. After adjustment for prior chemotherapy and cotreatment (paclitaxel, etoposide), all other baseline parameters were eliminated as risk factors. In the multivariate model, paclitaxel coadministration and prior cisplatin and/or carboplatin treatment were identified as independent risk factors for grade 2-4 neurotoxicity. The found associations could be anticipated and this unfortunately does not add much to our knowledge of cisplatin-induced neuropathy. Both paclitaxel and cisplatin are neurotoxic agents, and a combination of cisplatin with taxanes is known to result in increased neurotoxicity [32, 33]. Furthermore, cisplatin-induced neurotoxicity is mainly dependent on the cumulative cisplatin dose [29-31]. However, despite an increased risk of neurotoxicity in the platinum pretreated patients, severe neurotoxicity necessitating treatment discontinuation rarely occurred. This is in concordance with a previous study demonstrating that patients with absent or mild signs of neuropathy after prior treatment with cisplatin to a cumulative dose of 400-450 mg/m^2 can be retreated with six cycles of cisplatin 50-70 mg/m^2 weekly with only a minimal risk of significant neurotoxicity, not different from that in carboplatin pretreated patients [34].

Ototoxicity is another major side effect of cisplatin chemotherapy, and is probably caused by cisplatin-induced degeneration of the hair cells of the cochlea. Previous studies have shown that ototoxicity is related to both cumulative and individual cisplatin dose [4, 35, 36]. In the present study, tinnitus occurred in 25% of the patients, 15% had subjective, symptomatic hearing loss, and in 2.5% weekly cisplatin treatment was not completed due to ototoxicity.

Anaemia was a predisposing factor for grade 3-4 ototoxicity (OR = 3.1, CI = 1.6-6.3). The pathophysiological background of this association is presently unknown. Others previously identified anaemia as a risk factor for cisplatin-induced ototoxicity [37]. They also found a relation with hypoalbuminaemia, which was a borderline prognostic factor (OR = 2.4, CI = 0.9-6.7, $P = 0.1$) in the present study on weekly cisplatin. It is noteworthy that age, sex, performance status, creatinine clearance and individual cisplatin dose (in the range 70-80 mg/m^2) were not associated with ototoxicity. Remarkably, in the present analysis, performance status was not associated with any chemotherapy-induced toxicity, but this is probably related to the selection of patients with good performance status to treat with dose-dense cisplatin chemotherapy.

An advantage of the weekly regimen is shortening of the treatment period from 18-24 weeks with standard treatment (six courses with intervals of 3-4 weeks) to 6-8 weeks with

weekly treatment using similar total cisplatin dose. On theoretical grounds it can be expected that weekly cisplatin treatment enhances antitumour activity. Indeed, weekly cisplatin in combination with either etoposide or paclitaxel was highly active and well tolerated in the patients with advanced ovarian cancer, and even in the case of platinum-refractory disease (defined as platinum treatment-free interval < 4 months) the objective response rate was in the order of 50% [12, 13]. This suggests that platinum resistance is a relative phenomenon that could be overcome by shortening the treatment interval and supports the use of weekly platinum treatment in patients with relapsed ovarian cancer. For other tumour types, however, the place of weekly cisplatin treatment remains to be determined.

In conclusion, in a large cohort of patients, we have demonstrated that weekly cisplatin at doses of 70-80 mg/m^2 administered in hypertonic saline is a feasible treatment option, even when combined with oral etoposide or i.v. paclitaxel. Predisposing factors for treatment-related toxicity differ from side effect to side effect.

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CHAPTER 4

Body-surface area-based dosing does not increase accuracy of predicting cisplatin exposure

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ABSTRACT

Purpose: Most anticancer drugs are dosed based on body-surface area (BSA) to reduce interindividual variability of drug effects. We evaluated the relevance of this concept for cisplatin by analyzing cisplatin pharmacokinetics obtained in prospective studies in a large patient population.

Patients and Methods: Data were obtained from 268 adult patients (163 males / 105 females; median age, 54 years [range, 21 to 74 years]) with advanced solid tumors treated in phase I/II trials with cisplatin monotherapy or combination chemotherapy with etoposide, irinotecan, topotecan, or docetaxel. Cisplatin was administered either weekly (n = 93) or once every 3 weeks (n = 175) at dose levels of 50 to 100 mg/m^2 (3-hour infusion). Analysis of 485 complete courses was based on measurement of total and non-protein-bound cisplatin in plasma by atomic absorption spectrometry.

Results: No pharmacokinetic interaction was found between cisplatin and the anticancer drugs used in combination therapies. A linear correlation was observed between area under the curves of unbound and total cisplatin ($r = 0.63$). The mean plasma clearance of unbound cisplatin (CL_{free}) was 57.1 ± 14.7 l/h (range, 31.0 to 116 l/h) with an interpatient variability of 25.6%. BSA varied between 1.43 and 2.40 m^2 (mean, 1.86 ± 0.19 m^2) with an interpatient variability of 10.4%. When CL_{free} was corrected for BSA, interindividual variability remained in the same order (23.6% versus 25.6%). Only a weak correlation was found between CL_{free} and BSA ($r = 0.42$). Intrapatient variability in CL_{free}, calculated from 90 patients, was 12.1 ± 7.8% (range, 0.30 to 32.7%).

Conclusion: In view of the high interpatient variability in CL_{free} relative to variation in observed BSA, no rationale for continuing BSA-based dosing was found. We recommend fixed-dosing regimens for cisplatin.

INTRODUCTION

In clinical oncology, dose calculations for cytotoxic drugs based on body-surface area (BSA) have become standard practice. The use of BSA has largely resulted from its use in the extrapolation of drug doses used in experimental animals to those considered safe as starting doses for phase I clinical trials in human cancer patients. However, a proper scientific rationale for BSA-based dosing of anticancer drugs in adults is lacking [1, 2]. One exception is docetaxel, for which BSA was reported to be a good predictor of drug clearance (CL) in a population pharmacokinetic model [3]. For many other drugs, including epirubicin [4] and oral topotecan [5], the pharmacokinetic and pharmacodynamic behavior cannot be predicted reliably by BSA, because several other factors, like intestinal absorption, kidney function, and activity of key enzymes in metabolic pathways, are more important denominators. For example, the finding that carboplatin CL is closely related to glomerular filtration rate has resulted in dosing of this agent according to creatinine CL by the use of an alternative dosing algorithm to achieve a target measure of systemic

exposure [6]. However, for most agents, including cisplatin, there still is no better method of dose individualization than the non-evidence-based (though accepted) use of BSA-adjusted dosing. The aim of the present study was to investigate the utility of BSA in dosing of the anticancer drug cisplatin.

Cisplatin (*cis*-diamminedichloroplatinum) is a frequently applied agent with a broad spectrum of activity against solid tumors, including testicular, ovarian, bladder, lung, and head and neck cancers. With the use of optimal hydration measures, including supplementation of potassium and magnesium, the dose-limiting toxicity of cisplatin has changed from nephrotoxicity toward neurotoxicity and ototoxicity. Myelosuppression is generally moderate. Because of this toxicity profile, there is no useful short-term clinical marker for dose-limiting toxicity and dose adjustment. Earlier studies have shown that the area under the plasma concentration-time curve (AUC) of unbound cisplatin was significantly related to important pharmacodynamic endpoints [7-11]. For example, the AUC of free cisplatin and the platinum-DNA adduct formation measured in leukocytes were strongly correlated. The same applies to the grade of thrombocytopenia (which proved to be a dose-limiting side effect of weekly administration of cisplatin at a dose of 80 mg/m^2), as well as to the tumor response [12].

Here, we have analyzed pharmacokinetic data of 268 adult cancer patients who were treated with either cisplatin monotherapy or cisplatin-based combination therapy in several prospective studies. Intra- and interpatient variability in CL of total and free cisplatin was determined. In addition, the interpatient variability in BSA was calculated and compared with the interindividual variability in pharmacokinetic behavior of cisplatin.

PATIENTS AND METHODS

Patient selection

All patients studied had a confirmed diagnosis of malignant solid tumor and were treated with cisplatin monotherapy or cisplatin-based combination therapy (with either oral etoposide [13], intravenous (i.v.) irinotecan [14, 15], oral topotecan [16, 17], or i.v. docetaxel [18]) in clinical trials that included pharmacokinetic analysis of cisplatin. Detailed clinical and pharmacologic profiles have been documented previously [13-19]. According to the inclusion criteria of these trials, all patients were 18 to 75 years of age with an Eastern Cooperative Oncology Group performance status ≤ 2, had no previous anticancer therapy for at least 4 weeks, and had adequate hematopoietic (absolute neutrophil count ≥ 1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l), hepatic (total serum bilirubin ≤ 1.25 times the upper limit of normal and AST and ALT levels ≤ 2.5 times the upper limit of normal or ≤ 5.0 times in case of liver metastases), and renal function (creatinine CL ≥ 60 ml/min) at the time of study entry.

Drug administration

In all treatment schedules, cisplatin powder (Platosin; Pharmachemie, Haarlem, the Netherlands) was dissolved in 250 ml of 3% (weight-to-volume ratio [w/v]) hypertonic saline and administered as a 3-hour continuous i.v. infusion. The drug was administered at doses ranging from 50 to 100 mg/m^2, with treatment cycles repeated every week or every 3 weeks. For prevention of cisplatin-induced renal damage, a standard prehydration infusion with 1 l of 0.9% (w/v) isotonic saline or a mixture of 5% (w/v) dextrose and isotonic saline was used, as well as posthydration with at least 3 l of saline or dextrose-saline supplemented with potassium chloride (20 mmol/l) and magnesium sulfate (2 g/l). Antiemetic prophylaxis consisted of a $5HT_3$ antagonist in combination with dexamethasone. Diuretics were not administered routinely.

Clinical samples

Blood samples for pharmacokinetic analysis were drawn from the arm opposite to the infusion site during the first and (if required by protocol) during the second and third treatment course on the day of drug administration and were collected in 4.5-ml glass tubes containing lithium heparin as anticoagulant. Samples were collected immediately before the infusion, during (i.e. 1 and 2 hours after the start of the infusion), at the end of infusion (approximately 3 hours), and 0.5, 1, 2, 3, and 18 hours after the end of cisplatin infusion. Immediately after collection, samples were centrifuged to obtain the plasma fraction (3000 x *g* for 10 minutes). Next, 500-µl aliquots of the plasma supernatant were added to 1.0 ml of ice-cold (-20°C) ethanol. After vortex mixing for 10 seconds, samples were stored at -80°C until the day of analysis.

Analytic methods

Plasma concentrations of unbound and total cisplatin were determined by a validated flameless atomic absorption spectrometric procedure based on measurement of platinum atoms as described elsewhere [16]. For measurement of unbound cisplatin, 500-µl aliquots of plasma were extracted with 1.0 ml of neat, ice-cold ethanol in a 2-ml polypropylene vial (Eppendorf, Hamburg, Germany). The plasma supernatant was collected by centrifugation at 23,000 x *g* for 5 minutes at 4°C and transferred to a clean tube. A volume of 600 µl was evaporated to dryness under nitrogen at 60°C, and the residue was reconstituted in 200 or 600 µl of water containing 0.2% (volume-to-volume ratio) Triton X-100 and 0.06% (w/v) cesium chloride by vigorous mixing. A volume of 20 µl was eventually injected into the spectrometer. For determination of the total cisplatin concentrations, 100 µl of plasma was added to 900 µl of water containing 0.2% (volume-to-volume ratio) Triton X-100 and 0.06% (w/v) cesium chloride, followed by vortex mixing for 10 seconds. Of this solution, a volume of 20 µl was injected into the spectrometer. Samples were analyzed using a Perkin Elmer 4110 ZL Spectrometer (Perkin Elmer,

Überlingen, Germany) with Zeeman-background correction using peak area signal measurements at a wavelength of 265.9 nm and a slid width of 0.7 nm. Drug concentrations were determined by interpolation on linear calibration curves, constructed in blank human plasma, by least-squares regression of response values versus $1/x^2$. The mean percentage deviations from nominal values (accuracy) and precision (within-run and between-run variability) were always less than 15%.

Data analysis

Individual plasma concentrations of unbound and total cisplatin were fit to a one-compartment linear model with extended least-squares analysis with a weighting factor of $1/y$ using the software package Siphar 4.0 (InnaPhase, Philadelphia, PA, USA). The AUC of cisplatin was calculated to the last sampling time point (C_{last}) using the linear trapezoid method and extended to infinity by addition of C_{last}/k_{term}, where k_{term} is the slope obtained by log-linear regression of the final plasma concentration values. The apparent CL of unbound (CL_{free}) and total cisplatin (CL_{tot}) were calculated by dividing the dose per squared meter of BSA by the observed AUC values, expressed in l/h/m^2. The absolute CL values, expressed in l/h, were calculated by dividing the absolute dose (in milligrams) by the respective AUC values. After studying the entire patient population, patients were also divided into several groups. First, sex was studied separately; second, patients were classified into three different BSA groups: BSA less than 1.7 m^2, BSA between 1.7 and 2.0 m^2, and BSA more than 2.0 m^2, respectively.

Statistical evaluation

All pharmacokinetic parameters are reported as mean values ± standard deviation (SD), unless reported otherwise. Potential relationships between evaluated parameters were assessed by univariable or multivariate linear-regression analysis and Pearson's correlation coefficient (r) using the NCSS package (Version 5.X; J.L. Hintze, East Kaysville, UT, USA, 1992). Interpatient differences in pharmacokinetic parameters were calculated by defining the coefficient of variation, expressed as the ratio of the SD and the observed mean value. Similarly, values for intrapatient variability in cisplatin CL were obtained from patients who had received three pharmacokinetically assessable treatment courses. Variability in kinetic parameters between treatment courses or between the various cotreatment regimens was evaluated by the Wilcoxon signed-rank test or one-way analysis of variance (ANOVA) after testing for normality. ANOVA was also used to compare differences in body-size normalized CL among the different BSA categories with the Bonferroni correction for multiple comparisons. The Kruskal-Wallis statistic followed by a Dunn's multiple comparison test was applied for comparison of kinetic variables between cisplatin dose levels. Probability values of less than 0.05 were considered statistically significant.

RESULTS

Patient population

A total of 268 patients (163 males and 105 females; median age, 54 years [range, 21 to 74 years]), were studied in the present analysis (Table 1). The predominant disease types were non-small-cell lung cancer (n = 80 patients), colorectal cancer (n = 55), head and neck cancer (n = 42), and carcinoma of unknown primary (n = 35). The patients received single-agent cisplatin (n = 17) or cisplatin in combination with either docetaxel (n = 61), etoposide (n = 76), irinotecan (n = 57), or topotecan (n = 57). In total, 485 cycles were available for pharmacokinetic analysis.

Table 1: Patient demographics

Characteristic		No. of patients
Total number		268
Number of treatment courses	485	
Age, years		
Median	54	
Range	21-74	
Sex		
Male		163
Female		105
Primary tumor site		
NSCLC		80
Colorectal		55
Head and neck		42
CUP		35
Miscellaneous		56
Concomitant therapy		
Docetaxel		61
Etoposide		76
Irinotecan		57
Topotecan		57
None		17
Cisplatin dose		
50 mg/m^2		23
60 mg/m^2		12
70 mg/m^2		76
75 mg/m^2		80
80 mg/m^2		62
100 mg/m^2		15

NSCLC, non-small-cell lung cancer; CUP, carcinoma of unknown primary site.

Cisplatin pharmacokinetics

In line with previous findings [12], concentration-time profiles of unbound and total cisplatin could be best fitted to a one-compartment model with elimination characterized by decay in an apparent mono-exponential manner (Figure 1). By plotting all 485 kinetic data sets, a strong linear relationship was observed between the AUCs of unbound and total cisplatin (AUC_{tot} = [15.7 ± 1.48] + [7.49 ± 0.572] x AUC_{free}; r = 0.62; Figure 2). Because the fraction of unbound cisplatin to total cisplatin AUC values seemed to be constant amongst patients (overall mean, 0.074 ± 0.016; range, 0.035 to 0.147) and the previous observations that exposure measures based on unbound cisplatin are most closely associated with pharmacodynamic outcome [7-12], we focused on these measures in further analyses. In univariable and multivariate linear-regression analysis, it was observed that cytotoxic comedication, age, disease, and drug dose (in milligrams or milligrams per square meter; Figure 3) were all unrelated to CL_{free} ($r < 0.05$). Using one-way ANOVA, neither the coadministered drugs (etoposide, irinotecan, topotecan, or docetaxel), nor the administered cisplatin dose significantly influenced absolute (liters per hour) CL_{free} (P = 0.72 and P = 0.54, respectively). However, statistically significant differences in CL_{free} were noted between sexes ($P < 0.0001$); males had approximately 15% faster absolute CL_{free} than females (60.1 ± 13.9 versus 52.4 ± 14.6 l/h; mean difference [± SE], 7.65 ± 1.77 l/h; 95% confidence interval, 4.17 to 11.1 l/h). In addition, a significant difference was observed in BSA between males (mean, 1.93 ± 0.178 m^2; range, 1.45 to 2.40 m^2) and females (mean, 1.75 ± 0.161 m^2; range, 1.43 to 2.27 m^2) in the present study ($P < 0.00001$). However, the apparent CL of unbound cisplatin remained significantly different even when expressed relative to BSA (33.2 ± 6.94 versus 28.9 ± 7.69 l/h/m^2; $P < 0.001$).

Kinetic variability and role of BSA

In the entire patient population, CL_{free} ranged between 31 and 116 l/h (mean, 57.1 ± 14.7 l/h), with an interpatient variability of 25.6%. However, in these 268 patients, BSA varied between 1.43 to 2.40 m^2 (mean, 1.86 ± 0.19 m^2), with an interpatient variability of no more than 10.4%. When CL_{free} was corrected for BSA, the individual variability remained in the same order (i.e. 23.6% versus 25.6%). Furthermore, only a weak correlation was found between CL_{free} and BSA (CL_{free} = [31.80 ± 4.225] x BSA + [-1.985 ± 7.897]; r = 0.42), with large variability in CL_{free} across all studied BSA values in the 90 patients with three pharmacokinetically assessable courses (Figure 4). Statistically significant differences in CL_{free} for the three studied BSA groups (i.e. < 1.7 m^2, between 1.7 and 2.0 m^2, and > 2.0 m^2) were noted, with mean values of 49.7 ± 14.4, 55.7 ± 11.3, and 65.4 ± 16.2 l/h, respectively ($P < 0.05$, ANOVA followed by a Dunn's test). The interpatient variabilities for these groups were 29.0% (n = 59), 20.2% (n = 133), and 24.8% (n = 76), and these values remained unaltered after correction for individual BSA values (29.7%, 19.8%, and 24.5%, respectively).

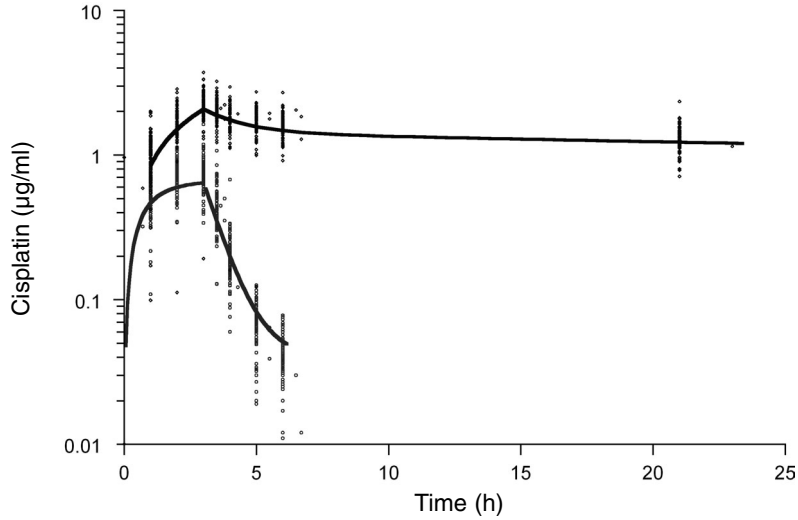

Figure 1
Plasma concentration-time profiles of unbound cisplatin (○) and total cisplatin (●) in 76 patients receiving cisplatin at a dose of 70 mg/m^2.

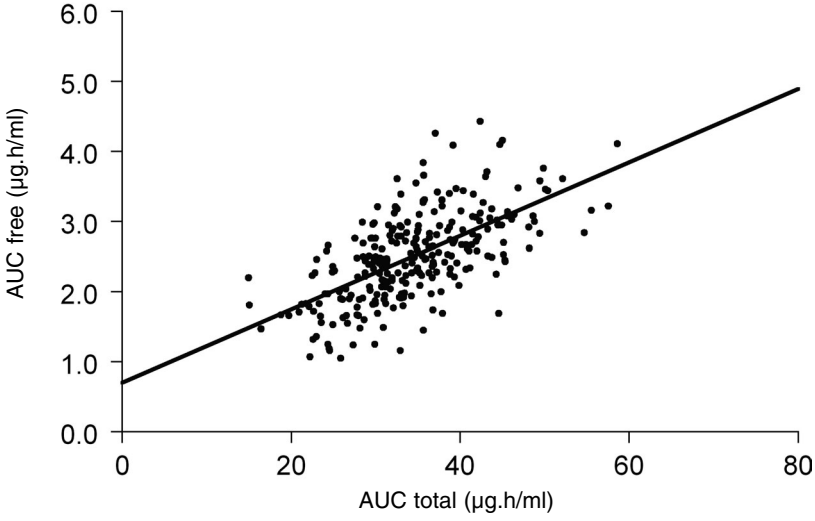

Figure 2
Relationship between the AUCs of unbound and total cisplatin in data obtained from first treatment courses of 268 patients.

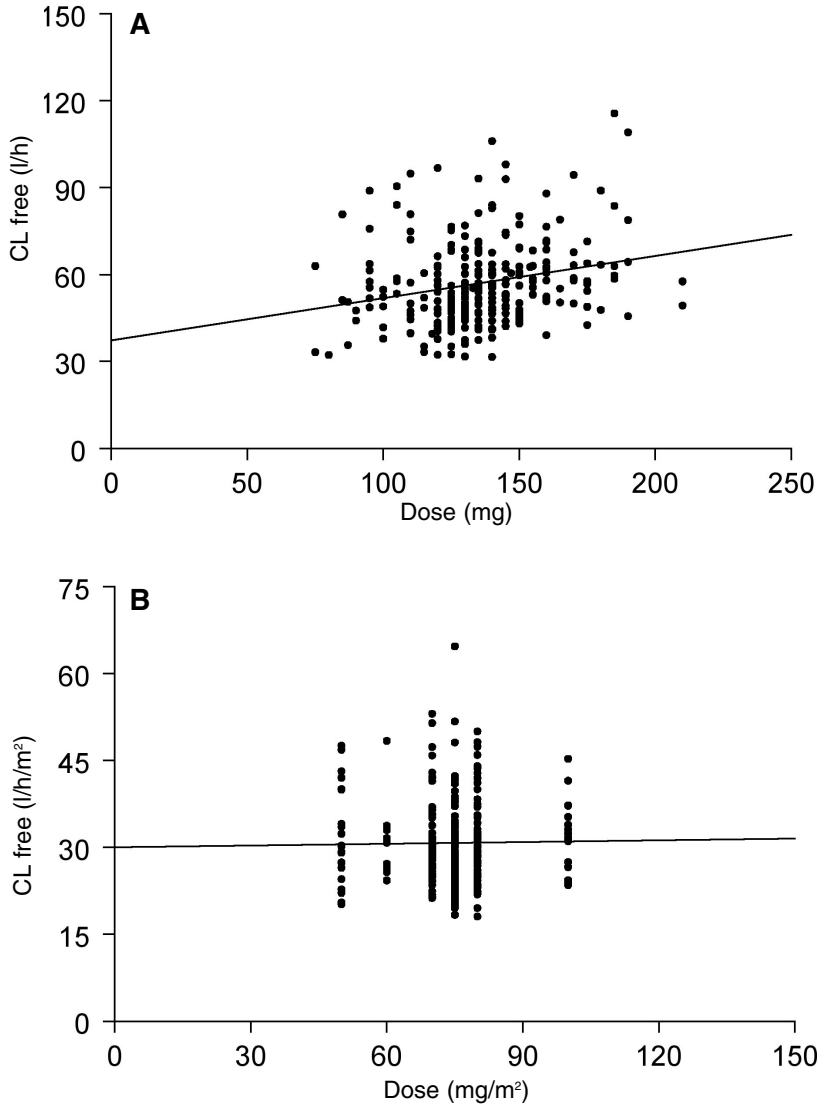

Figure 3
(A) Relationship between the absolute cisplatin dose (milligrams) and the absolute clearance of unbound cisplatin (expressed in liters per hour), and **(B)** the relationship between the cisplatin dose (milligrams per square meter) and the apparent clearance of unbound cisplatin (expressed in liters per hour per square meter). Data were obtained from 268 pharmacokinetically assessable patients.

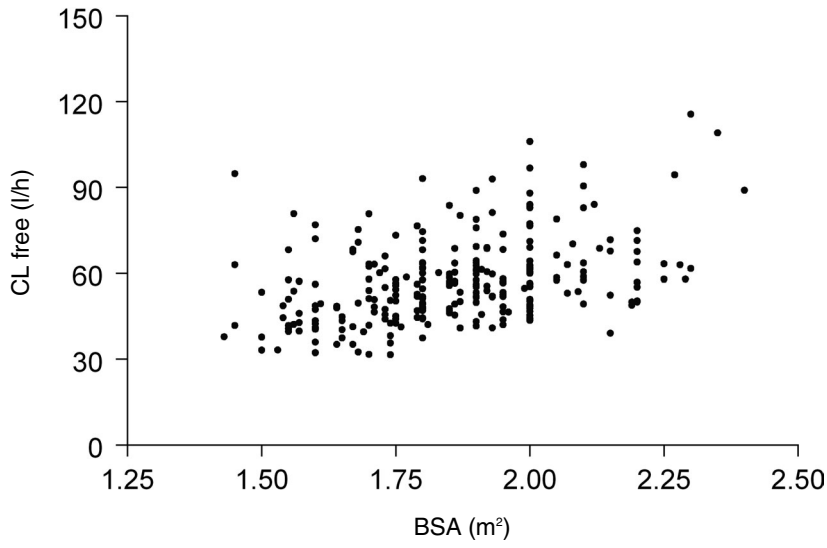

Figure 4
BSA versus absolute clearance of unbound cisplatin (expressed in liters per hour). Data were obtained from 268 pharmacokinetically assessable patients.

The CL_{tot} as measured during the first treatment cycle in all patients ranged from 2.30 to 7.98 l/h (mean, 4.09 ± 0.91 l/h), with an interpatient variability of 22.2%. Intrapatient variability in CL_{free} was calculated from 90 patients who had complete pharmacokinetic monitoring during three cycles of chemotherapy. The intrapatient variability in CL_{free} ranged from 0.30% to 32.7% (median, 10.7%; mean, 12.1 ± 7.8%). A significant carryover effect was observed for total cisplatin concentrations, particularly in patients on the weekly schedule, precluding accurate calculation of intrapatient variability in CL. For unbound cisplatin, no alteration in CL was observed after multiple courses ($P = 0.31$).

DISCUSSION

The current clinical practice for dosing of the anticancer agent cisplatin is based on BSA of the individual patient. This use, in turn, is explained by the assumption of a narrow relationship between the CL of the drug and BSA. However, no data in the literature exist to support this assumption for cisplatin. In the present report, we have studied the relationship between cisplatin CL and BSA in a group of 268 patients who were treated with cisplatin in phase I/II clinical studies.

In line with previous findings, the concentration-time curves of unbound cisplatin and total cisplatin (i.e. bound to plasma proteins [mainly albumin] plus unbound) did not run parallel, suggesting that protein-binding is essentially irreversible [20, 21]. It has been shown that the drug is primarily eliminated by the kidneys, although within 24 hours of treatment cisplatin exhibits relatively low recovery in urine (approximately 11 to 32%) [22]. This observation probably reflects the extensive binding of reactive platinum metabolites to plasma proteins and tissues and implies that renal CL is relatively unimportant, at least during the initial phases of drug CL. In view of this restrictive CL of cisplatin, it has been recommended to use unbound cisplatin-concentration data for representative calculation of pharmacokinetic parameters (AUC values and CL). Indeed, as mentioned previously, it has been shown that correlations exist between clinical effects and kinetic parameters of unbound cisplatin [7-12]. Thus the interindividual variability in CL of the pharmacologically active unbound cisplatin is an important determinant of treatment outcome. Furthermore, it has been demonstrated in several studies (in which patients received a constant dose in milligrams per square meter) that inappropriate cisplatin AUC was the single most important determinant of toxicity or relapse [12]. Here, we found that the coefficient of variation for cisplatin CL expressed in absolute measures or relative to BSA were both in the same order (23.6% versus 25.6%) and that BSA was poorly related to unbound cisplatin CL. Thus, given the frequency with which cisplatin AUC will exceed thresholds associated with undesired outcomes even when dose is adjusted for BSA, unbound cisplatin monitoring and/or the need to adjust cisplatin dose based on AUC measured in the individual patient may be required regardless of body-size measures. On the other hand, it is noteworthy that the interindividual variability in BSA of the patients was only 10.4%, indicating that an effect of BSA on cisplatin CL was measurable but not highly contributory. This strongly suggests that other (unknown) factors than BSA could be considered more important predictors of CL and AUC.

Using univariable and multivariate regression analysis, we found that various demographic variables or other covariates, including comedication, disease type, and drug dose, were not related to unbound cisplatin CL, which is in agreement with previous population models for cisplatin pharmacokinetics [23, 24]. Interestingly, it was observed in these models that only BSA and infusion duration impacted on CL, although interindividual variability as well as residual variability remained large (approximately 23 to 36%, respectively). The finding that age is not a covariate on CL is at odds with at least one recent observation of a significant negative correlation between age and CL for both total cisplatin and unbound drug [25]. Using a general linear model, these authors found that age was independent of sex and tumor type as a predictor of cisplatin kinetics and suggested that with increasing age (a known determinant of renal function), cisplatin elimination by the kidneys might be reduced, leading to a reduction in overall CL. The basis for these discrepant findings is currently unknown, although they may relate, for example, to patient-specific differences in the studied populations.

Interestingly, we observed that male patients had approximately 15% faster CL of unbound cisplatin compared with female patients, whose CL values were 9.0% lower than

the mean of all patients. The reason for a lower CL of unbound cisplatin in females is not clear, although it does not seem to be related to differences in prior chemotherapy. Previous studies have revealed similar differences for several other anticancer agents, including irinotecan and topotecan [26], and that major factors responsible for sex-dependent pharmacokinetics are related to differences in body composition, renal elimination, and hepatic function [27]. Indeed, we found a significant difference in BSA between males and females, although most importantly, the apparent CL of unbound cisplatin remained significantly different even when expressed relative to BSA. As studies have identified kinetic thresholds for severe toxicity and antitumor activity, the current data suggest that an apparent decrease in cisplatin CL in females could result in enhanced toxicity after fixed-dosing regimens (in milligrams per square meter) as compared with males. However, the relatively small difference found in this analysis indicates that it might not be of clinical relevance and suggests that this issue should be investigated further.

The variability in unbound cisplatin CL in the patients we studied is similar to that reported for cisplatin administered to 26 cancer patients at a dose of 80 mg/m^2 by infusion over 2, 3.5, or 4 hours (23.6% versus 22.9%) [24]. In general, variability in absolute CL of most anticancer drugs, including docetaxel, etoposide, irinotecan, paclitaxel, and topotecan, is substantially larger (i.e. > 30%) than that observed here for cisplatin. One reason for this might be that these agents are primarily eliminated by hepatic P450 oxidative metabolic (phase I) enzymes, the expression of which is highly variable among individuals (up to six-fold) and which is sensitive to induction and inhibition by various other xenobiotics. It is also noteworthy that CL of several other platinum analogs (e.g. carboplatin and oxaliplatin) is predominantly driven by glomerular filtration, which may explain increased kinetic variability as compared with cisplatin [28].

The intrapatient variability in the AUC and CL of total and unbound cisplatin, measured in a subset of 90 patients sampled during three courses, was also exceptionally low (approximately 12%). Part of this intraindividual variability, particularly for total cisplatin, was caused by a decrease in CL after repeated administration of cisplatin, suggesting that this variation might even be overestimated. The mechanism of decreased cisplatin CL after repeated administration is not completely understood. One explanation is that part of the observed increase in AUC (and hence decrease in CL) may be artificial because drug levels have not fallen to zero at the time of next administration (i.e. as a result of carryover effects).

It is concluded that cisplatin CL is related to BSA. The relation, however, is weak and other presently unknown factors are probably more important. The effect of BSA on pharmacokinetics was measurable but had little, if any, predictive ability. In view of the relatively high interindividual variability in the CL of unbound drug and the small range in observed BSA in the entire patient population, cisplatin can be added to the list of anticancer agents where BSA-adjusted dosing does not seem more accurate. A careful study to identify alternative clinical or laboratory parameters with predictive value toward cisplatin CL and AUC by a population approach to pharmacokinetic modeling using NONMEM (S.L. Beal and L.B. Sheiner, San Francisco, CA, USA) is currently in progress.

Unless better predictors for unbound drug CL are identified, it is recommended (in the therapeutic dose range of 50 to 100 mg/m^2) to apply fixed-dosing regimens for cisplatin in adult cancer patients. Currently, a further randomized clinical study is being conducted to fully explore the advantages of this approach, in which simultaneously the need for potential dosage adjustments at extreme BSA values will be investigated.

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CHAPTER 5

Population pharmacokinetics of cisplatin in adult cancer patients

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Submitted

ABSTRACT

Purpose: To characterize the pharmacokinetics of the anticancer agent cisplatin, and explore the influence of patient covariates and interoccasion variability on drug disposition.

Experimental Design: Data were obtained from 285 patients (519 complete curves; 3483 plasma samples) who received the drug as a 3-hour intravenous infusion at a mean dose of 144 mg (range, 75 to 210 mg). The population model was built with the use of NONMEM, performing generalized additive modeling (GAM) to identify candidate covariates (including body-surface area (BSA), age, sex, height, weight, hematocrit, total protein, albumin, serum creatinine, and creatinine clearance), and using a backward deletion protocol to obtain the final models for clearance (CL) and volume of distribution (V).

Results: The final model was a 1-compartment linear model with BSA (in m^2) as the only significant covariate that impacted on both CL and V: TVCL (in l/h) = 51.7 + 26.3 x (BSA – 1.855) and TVV (in l) = 41.1 + 4.15 x (BSA – 1.855), where TVCL and TVV are referred to as typical values that could be used *a priori* in dosage regimen design. The coefficient of intervariability estimates for CL and V were 16.82% and 20.35%, respectively.

Conclusion: A population pharmacokinetic model for cisplatin has been developed that incorporates measures of body size to predict clearance. In this patient population, cisplatin pharmacokinetics was not associated with age, sex, and measures of renal dysfunction.

INTRODUCTION

Cis-diamminedichloroplatinum (cisplatin) is a commonly used anticancer drug with a broad spectrum of activity against malignant solid tumors, including lung, head and neck, bladder, germ cell, ovarian, endometrial, and cervical cancer [1]. In the conventional 3- or 4-weekly treatment regimens, dose-limiting side effects include renal tubular dysfunction, peripheral neuropathy, and hearing loss (ototoxicity), whereas hematological toxicity becomes dose-limiting in the more dose-dense, weekly regimens [2]. Nausea and vomiting -once predominant side effects of cisplatin- have become manageable with a combination of dexamethasone and 5-hydroxytryptamine-3-receptor antagonists [1-3].

Although cisplatin-induced toxicity is dose-dependent, the individual susceptibility to side effects varies considerably. As for most other anticancer agents, the administered dose of cisplatin is normalized by a patient's BSA. However, for most anticancer agents clearance is poorly correlated to body-size measures and hence, the routine use of BSA as the only independent variable considered in drug dosing is questionable [4-6]. Previous studies have revealed significant relationships between cisplatin pharmacokinetics and the likelihood of tumor response and toxicity [7]. Hence, availability of a useful model

incorporating factors affecting drug clearance that could be used to predict or adapt appropriate doses of cisplatin is required.

Standard noncompartmental pharmacokinetic evaluation demonstrated that exposure to cisplatin is dose-proportional over a wide dose range [6]. We have also shown that cisplatin disposition is unaffected by concomitant administration of the chemotherapeutic agents etoposide [7], docetaxel [8], irinotecan [9-11], and topotecan [12, 13]. The data from these trials were collected prospectively to characterize the pharmacokinetics of cisplatin in a broad patient population under general clinical conditions. Here, we report the population pharmacokinetic model-building process, and the exploration for demographic subpopulations for which dose adjustment may be needed.

PATIENTS AND METHODS

Patient eligibility

All patients studied had a confirmed diagnosis of a malignant solid tumor and were entered in five different clinical phase I trials [7, 8, 10, 12, 13], with cisplatin given alone or as part of a combination chemotherapy regimen. According to the inclusion criteria of these trials, all patients were 18 to 75 years of age with an Eastern Cooperative Oncology Group performance status 0-2, had no previous anticancer therapy for at least 4 weeks, and had adequate hematopoietic (absolute neutrophil count $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l), hepatic (total serum bilirubin $\leq$ 1.25 x the upper limit of institutional normal values and serum transaminase levels $\leq$ 2.5 x the upper limit of institutional normal values or $\leq$ 5.0 x in case of liver metastases), and renal function (normal serum creatinine and/or creatinine clearance $\geq$ 60 ml/min) at the time of study entry. None of the patients used any other comedication known to interfere with cisplatin pharmacokinetics. All patients were treated at the Erasmus MC – Daniel den Hoed Cancer Center (Rotterdam, the Netherlands), the study protocols were reviewed and approved by the Erasmus MC review board and patients gave written informed consent to participate. The overall safety, tolerance, and efficacy results and a traditional pharmacokinetic analysis have been reported in detail previously [7-13].

Drug administration

Cisplatin powder (Pharmachemie, Haarlem, the Netherlands) was dissolved in 250 ml of a sterile, hypertonic solution containing 3% (weight-to-volume ratio [w/v]) sodium chloride and was administered as a 3-hour continuous intravenous infusion at doses ranging from 50 to 100 mg/m^2 with treatment cycles repeated every week or every 3 weeks. Antiemetic prophylaxis consisted of a 5-hydroxytryptamine-3-receptor antagonist in combination with dexamethasone. For prevention of cisplatin-induced renal toxicity, a standard prehydration infusion with 1 l of normal isotonic 0.9% (w/v) sodium chloride or

5% (w/v) dextrose – 0.9% (w/v) sodium chloride (1:1, volume-to-volume ratio) was used, as well as a posthydration regimen of 3 l of the same solution containing potassium chloride (20 mmol/l) and magnesium sulfate (2 g/l). Diuretics were not administered routinely.

Sampling and drug analysis

Since the non-protein-bound drug fraction is considered to be the pharmacologically active component, we focused on measurement of unbound cisplatin concentrations. All analytical measurements were performed at the Laboratory of Translational and Molecular Pharmacology of the Erasmus MC – Daniel den Hoed Cancer Center using a validated assay based on ethanolic protein precipitation followed by atomic absorption spectrometry [10]. A previous direct comparison of this technique with the more routinely used methods based on ultrafiltration revealed that the recovery of unbound cisplatin observed for ethanol-treated samples was not significantly different from that recorded for sample preparation using ultrafiltrates [14].

Blood samples were drawn from the arm opposite to the infusion site and collected in 4.5-ml glass tubes containing lithium heparin as anticoagulant. Samples were collected immediately before drug infusion, at 1 and 2 hours after the start of infusion, at 5 minutes before the end of infusion, and at 0.5, 1, 2, 3, and 18 hours after the end of infusion. In a limited number of patients, additional samples were obtained at 1.5 and 5 hours after the end of infusion. Plasma was separated by centrifugation at 3,000 x *g* for 10 minutes, and 500-µl aliquots of plasma were immediately extracted with 1,000 µl of neat, ice-cold (-20°C) ethanol in a 2-ml polypropylene vial. After a 2-hour incubation at -20°C, the supernatant was collected by centrifugation at 23,000 x *g* for 5 minutes at 4°C and transferred to a clean vial. A volume of 600 µl was evaporated to dryness under nitrogen at 60°C, and the residue was reconstituted in 200 or 600 µl of water containing 0.2% (volume-to-volume ratio) Triton X-100 and 0.06% (w/v) cesium chloride by vigorous mixing for 10 seconds. A volume of 20 µl was eventually injected into the flameless atomic absorption spectrometer. Samples were analyzed for platinum-containing species with a Perkin Elmer 4110 ZL Spectrometer (Perkin Elmer, Norwalk, CT, USA) with Zeeman-background correction using peak area signal measurements at a wavelength of 265.9 nm and a slid width of 0.7 nm. The injection temperature was set at 20°C. Drug concentrations were determined by interpolation on linear calibration curves constructed in blank (drug-free) human plasma obtained from healthy volunteers, by a linear least-squares regression analysis using a weight factor of $1/X^2$. The mean percentage deviation from nominal values (accuracy) and precision (within-run and between-run variability) were always less than 15%.

Pharmacokinetic model

Population pharmacokinetic analysis was performed with the population mixed-effect modeling computer program NONMEM (Version V with double precision; S.L. Beal and L.B. Sheiner, University of California, San Francisco, CA, USA). Development of the population model was performed in three distinct steps [15], as follows: (*i*) development of an initial covariate-free model using the first-order conditional estimation method within NONMEM and Bayesian estimation of individual pharmacokinetic parameters; (*ii*) evaluation of the influence of patient characteristics; and (*iii*) optimization of the final model.

The database incorporated all cisplatin samples collected during the study protocols. The pharmacokinetic parameters estimated were CL and V. Interpatient variability (η) and residual or intrapatient variability (ε) were evaluated through alternate statistical models (i.e. additive, constant coefficient of variation, and exponential). Interoccasion variability (IOV) was considered as well since a substantial number of patients underwent pharmacokinetic sampling on more than one treatment cycle, and it is obvious that pharmacokinetic parameters may vary randomly between study occasions. Therefore, ignoring IOV could result in biased population parameter estimates and the selection of inappropriate models for population data. Identification of the best structural model was based on the objective function value from NONMEM output and on interpretation of diagnostic plots of weighted residuals versus predicted unbound cisplatin concentrations.

After the initial model was selected, empirical Bayesian estimates of the individual pharmacokinetic parameters were calculated (*posthoc* step in the NONMEM program). The effect of patient characteristics on the variables CL and V was then evaluated using generalized additive modeling (GAM) [16], which was performed with Xpose (Version 2.04) running within the S-plus (Version 2000) program. BSA, age, sex, height, weight, hematocrit, total protein, albumin, serum creatinine, and creatinine clearance were evaluated by analysis of the relationship between the patient variable or covariate and the empirical pharmacokinetic estimate using the Akaike's information criterion (AIC) [17]. An individual covariate was considered to significantly improve the model if its addition resulted in a decrease in AIC by a value of greater than 3.84 ($P < 0.05$). All significant covariates were added to the model and then removed one at a time in order of decreasing improvement in AIC, and only those that showed a significant contribution to the fit were considered and retained in the model. During this step, the level of statistical significance was chosen at $P < 0.001$, corresponding with a greater than 10.83 increase in the objective function value (-2 x the log likelihood function). Finally, model performance was assessed by graphic plots of (*i*) observed *versus* predicted unbound cisplatin plasma concentrations and (*ii*) weighted residuals *versus* predicted unbound cisplatin plasma concentrations randomly scattered around zero. This analysis was done in the software package JMP version 3.2.6 (SAS Institute, Carey, NC, USA).

RESULTS

Patient population

The patient characteristics are summarized in Table 1. A total of 519 treatment cycles from 285 patients was available for pharmacokinetic analysis. Of the 285 patients, 140 were also evaluated during a second treatment cycle, and 94 patients during a second and third cycle. The patients were treated with cisplatin given either alone (34 patients; 12%) or as cisplatin-based combination therapy with either oral etoposide (76 patients; 27%), intravenous docetaxel (61 patients; 21%), intravenous irinotecan (57 patients; 20%) or oral topotecan (57 patients; 20%). Cisplatin was administered at doses ranging from 50 to 100 mg/m^2 (mean dose, 144 mg; range, 75 to 210 mg), with treatment cycles repeated every week (93 patients; 33%) or every 3 weeks (192 patients; 67%).

Table 1: Patient demographics at baseline in cycle 1[a]

Characteristic	*Value*	
Number of patients studied	285	
Number of evaluable courses	519	
Sex		
Female	112	(39%)
Male	173	(61%)
Age (years)	54	(21–74)
Height (m)	1.73	(1.28–1.92)
Weight (kg)	72.5	(39.3–115)
Body-surface area (m^2)	1.85	(1.29–2.40)
Infusion duration (h)	3.00	(2.00–4.00)
Hematocrit (l/l)	0.39	(0.27–0.50)
Albumin (g/dl)	4.20	(2.50–5.50)
Total protein (g/dl)	7.40	(5.60–9.20)
Serum creatinine (µmol/l)	84	(52–146)
Creatinine clearance (ml/min)	76.2	(39.3–156)

[a] Continuous data are given as median with range in parenthesis, and categorical data as number of patients with percentage of the total population in parenthesis.

Initial parameter estimates

The final data set consisted of 4643 plasma samples, of which 3483 had concentrations with a value above the lower limit of quantitation of the analytical assay. The observed plasma concentrations of unbound cisplatin are shown in Figure 1. Development of the structural covariate-free model indicated that a linear, open 1-compartment model best fit the observed concentration-time data. Interpatient variability (η) for CL and V was modeled by a constant coefficient of variation in this best-fit structural model as follows:

$$CL = TVCL \times (1 + \eta_{CL})$$
$$V = TVV \times (1 + \eta_{V})$$

In these equations, CL and V are empirical Bayesian parameter estimates based on population values combined with the observed individual values for CL and V, respectively. TVCL and TVV are typical values for CL and V, respectively, which are determined from the population mean parameters; ηCL and ηV are measures of the difference between CL and TVCL, and V and TVV, respectively.

Residual or intrapatient variability (ε_{ij}) is a random variable assumed to have a population mean of zero. It was modeled as an additive term in the best-fit structural pharmacokinetic model ($Y = F + \varepsilon_{ij}$), and accounts for differences in observed and model-predicted unbound cisplatin concentrations in the individual patient. As mentioned earlier, blood sampling was obtained during one (OCC1), two (OCC2), or three treatment cycles per patient (OCC3). The model for interoccasion variability for CL (π_{CL}) and V (π_{V}) was modeled as follows:

$$CL = TVCL \times \exp[\eta\,(1) + \eta\,(3) \times OCC1 + \eta\,(5) \times OCC2 + \eta\,(7) \times OCC3]$$
$$V = TV \times \exp[\eta\,(2) + \eta\,(4) \times OCC1 + \eta\,(6) \times OCC2 + \eta\,(8) \times OCC3]$$

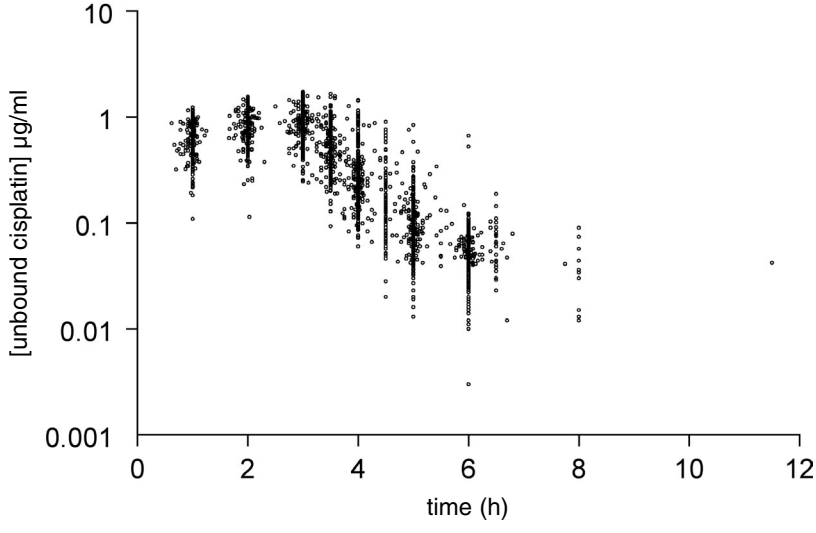

Figure 1
Observed plasma concentrations of unbound cisplatin after intravenous infusion of cisplatin to 285 patients (519 courses).

Demographic covariates and final model

The GAM analysis identified BSA, hematocrit and sex as candidate covariates influencing CL, whereas BSA and albumin were identified as candidate covariates influencing V. However, following forward addition and backward deletion strategies, both for CL and V, only BSA was maintained as a significant covariate in the final population pharmacokinetic model for cisplatin, as follows:

TVCL (l/h) = 51.7 + 26.3 x (BSA – 1.855)
TVV (l) = 41.4 + 4.15 x (BSA – 1.855)

The final pharmacokinetic model described the population and individual data well since the predicted concentrations of unbound cisplatin (in the range of 0.005 to 1.30 µg/ml) were highly correlated to the observed data (Figure 2). Although the model tended to underestimate concentrations above 1.30 µg/ml, data in this range represented only a minor 1.41% of the full data set (49 out of 3483). The overall regression equations are given by:

$Y = (0.9785 \pm 0.00852) \bullet X + (0.0252 \pm 0.00487)$ (population predictions; $R^2 = 0.791$)
$Y = (0.9977 \pm 0.00419) \bullet X + (0.0209 \pm 0.00250)$ (individual predictions; $R^2 = 0.942$)

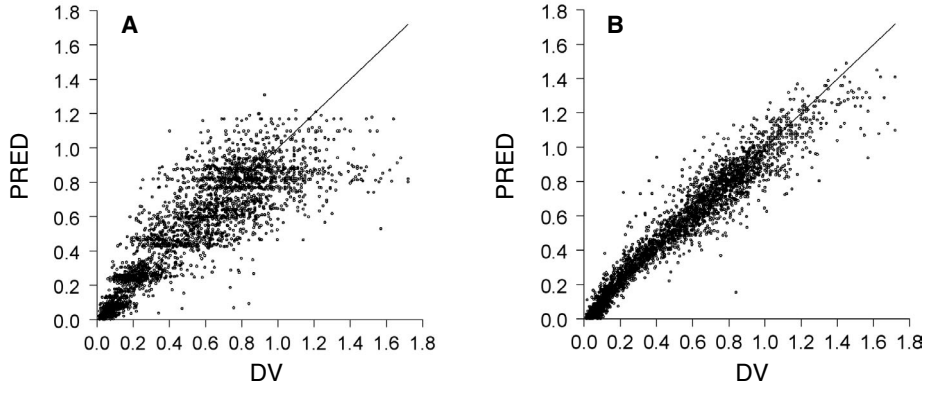

Figure 2
Observed concentrations (DV, dependent variable) versus the population predictions (PRED; panel A) and individual predictions (IPRED; panel B) of unbound cisplatin. All concentration units are µg/ml. The solid lines indicate the lines of identity.

In the population predictions, the residuals (i.e. the difference between the observed and final model-predicted concentrations) had a mean (± standard deviation) value of 0.015 ± 0.167 µg/ml, with 90% of the residuals ranging from -0.172 to 0.209 µg/ml ($P > 0.99$ versus hypothesized mean = 0; Figure 3).

The clearance and volume of distribution of unbound cisplatin for a representative patient with a BSA value of 1.855 m^2 were 51.7 l/h and 41.4 l, respectively. After accounting for the covariate of BSA, the remaining interindividual variability for clearance was 16.82%. A summary of the variability estimates, including values for residual variance (σ^2), is given in Table 2.

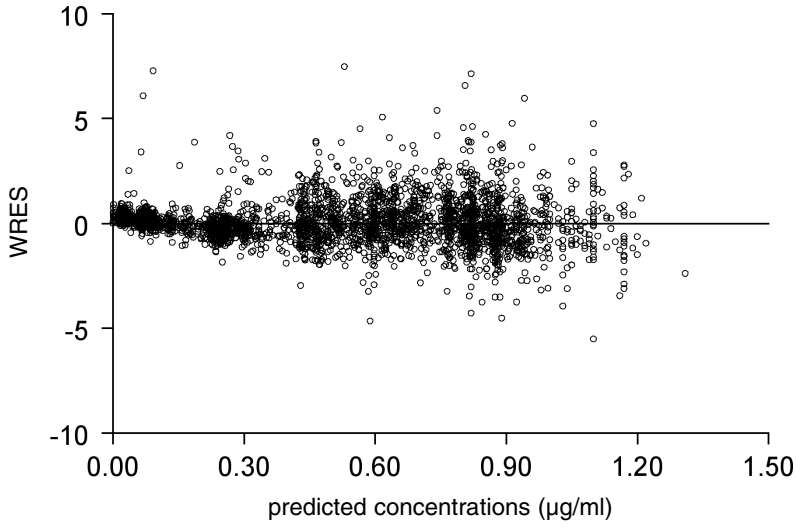

Figure 3
Weighted residuals (WRES) versus the predicted concentrations of unbound cisplatin.

Table 2: Summary of variability estimates

Parameter	η_{CL} (%)	η_V (%)	π_{CL} (%)	π_{CL} (%)	R(η)	R(π)	σ^2
Estimate	16.82	20.35	13.93	22.41	0.859	0.343	0.00989
SE	6.78	9.31	5.06	9.99	-	-	0.000698

CL, clearance; V, volume of distribution; η_{CL} and η_V, interindividual variability for CL and V, respectively; π_{CL} and π_V, interoccasion variability for CL and V, respectively; R(η), correlation between η_{CL} and η_V; R(π), correlation between π_{CL} and π_V; σ^2, residual variance; SE, standard error.

DISCUSSION

The present study was initiated through the results of a previous study on the relationship between cisplatin exposure and BSA, which demonstrated a significant correlation between the plasma clearance of unbound cisplatin and BSA. However, the magnitude of this correlation was considered insufficient to justify BSA-guided dosing of cisplatin [6]. This is not surprising if one considers the rather complex pharmacological behavior of cisplatin, which includes several processes that are unlikely to be dependent on BSA. During and shortly after intravenous administration of cisplatin, rapid renal excretion of unbound cisplatin takes place at a clearance rate approximately 5 to 10 times the glomerular filtration rate, suggesting that unbound cisplatin is excreted by the kidneys through an active tubular secretion process. However, only 20 to 35% of the administered dose can be retrieved in the urine during and after drug administration [18, 19]. This could be explained by progressive, strong and partially irreversible binding to plasma proteins (mainly albumin), whereas binding to cellular proteins and nucleic acids also occurs [20]. Protein binding and cellular toxicity are further influenced by the equilibrium between chlorinated and hydrated platinum species, the hydrated platinum compounds being more reactive and producing more cellular toxicity (especially renal tubular toxicity) [21]. Although exposure to cisplatin reflected by the AUC of unbound platinum is highly variable, close correlation has been demonstrated between *in vivo* DNA-adduct formation in leukocytes and AUC. Furthermore, AUC and DNA-adduct formation were significantly higher in patients with tumors responding to treatment than in patients not responding [18]. In view of this, and because AUC is determined by administered dose and drug clearance, we have evaluated a number of patient variables (i.e. age, sex, hematocrit, total protein, albumin, serum creatinine, creatinine clearance) in addition to common measures of body size (i.e. height, weight, BSA) on their influence on unbound cisplatin pharmacokinetics in a nonlinear mixed-effect model.

The population pharmacokinetic modeling was based on 519 cisplatin treatment cycles in a group of 285 patients. The best structural covariate-free model was a linear 1-compartment model with a constant coefficient of variation error model for interpatient variability and an additive error model for intrapatient variability. Since a total of 140 patients had blood sampling on two or three occasions, interoccasion variability was also taken into account. Interoccasion variability could be successfully modeled through an exponential error model, which helped in the selection of appropriate models for the population pharmacokinetic data.

Common anthropomorphic covariates were not found to influence cisplatin disposition to a clinically relevant extent, and BSA was identified as the only significant covariate on clearance and volume of distribution. This finding is in concordance with the two previous population pharmacokinetic studies presented by Hanada *et al*. [22] in 27 patients (dose, 60 to 100 mg/m^2 over 90 minutes) and Nagai *et al*. [23] in 26 patients (dose, 80 mg/m^2 over 2, 3.5 or 4 hours). The latter study also demonstrated that unbound cisplatin clearance was schedule dependent, with clearance increasing with a decrease in infusion duration,

in line with earlier observations [24, 25]. In the present study, cisplatin was administered as a 3-hour infusion, and the infusion duration was constant within each patient. Height and weight had no additional value to BSA in the population model for cisplatin. It is noteworthy to point out that, although there was a statistically significant influence of BSA on cisplatin clearance, the relationship was very shallow and data showed considerable scatter. Specifically, cisplatin clearance increased by only 2.63 l/h per one-tenth unit of body-size and hence, a 0.10-m^2 increase in BSA was associated with a mere 5.09% increase in clearance. The interquantile range of BSA values observed in our patient population was 1.71 to 2.00 m^2, which suggests that 75% of treated adults will have a predicted cisplatin clearance in the range of 47.9 to 55.5 l/h. This range is clearly of very minor relevance against a background of interindividual variability in clearance of 17%. A similar argument can be made for the influence of BSA on the volume of distribution, suggesting that dose adjustment of cisplatin for body-size measures appears unnecessary. An exception would be the treatment of patients at extremes of BSA, like those observed in our group. As predicted by the population model, average 1.29-m^2 and 2.40-m^2 patients would have clearances of 36.0 and 66.0 l/h, respectively, which translates into a two-fold difference in systemic exposure to unbound cisplatin for a given intravenous dose.

Age had no significant influence on unbound cisplatin clearance, which is in line with reports describing a lack of age-dependent cisplatin nephrotoxicity [26, 27]. Although, on average, women have a 15% slower unbound cisplatin clearance than men [6], the addition of sex into the final population model did not result in substantial improvement. Hematocrit, total protein and albumin were introduced into the model because a relation with unbound drug clearance and volume of distribution was expected. Namely, during and after intravenous administration of cisplatin, progressive protein binding takes place mainly involving albumin but also other plasma proteins and intracellular proteins like hemoglobin. However, addition of these covariates to BSA did not lead to improvement of the model. The same applies to serum creatinine and creatinine clearance, although this could partly be explained by the fact that patients with moderate or severe renal dysfunction were excluded from the study protocols. Patients with moderate to severe renal impairment demonstrate aberrant pharmacokinetic profiles [28], and unbound cisplatin peak concentrations in such patients (above 2.0 µg/ml) have been linked to several markers of cisplatin-associated nephrotoxicity [29, 30]. In our population, model-predicted peak concentrations (median, 0.912 µg/ml; range, 0.266 to 1.49 µg/ml) were not related to pretherapy serum creatinine values, creatinine clearance, or the maximum percent decrease in creatinine clearance (median, 2.61%; range, -36.6 to 38.1%; n = 91 patients) following repeat administrations (not shown). The relatively low peak levels and the applied pre- and posthydration regimens likely contributed to the lack of significance in these relationships.

The final parameter estimates from the current population analysis approximate the average pharmacokinetic parameters of more traditional analyses, with mean clearance values of 51.7 l/h versus 56.3 l/h (range, 31.0 to 123 l/h; n = 391 patients; Ref. [6] and

unpublished data), respectively. The smaller range of observed clearance values as compared to the previous study, albeit in a similar patient population, is likely related to the present analysis representing a more robust modeling that is less influenced by sampling, analytical and/or dosing errors. After BSA as covariate was accounted for, the remaining interindividual variability for clearance was moderate at approximately 17%. At present, the causes for this variability are unknown. Inasmuch as cisplatin clearance is primarily dictated by near-covalent binding to serum proteins and renal elimination pathways, the variability may reflect, in part, kinetic processes that remain undetected by the analytical procedure employed, which is based on simultaneous measurement of all platinum-containing species.

In conclusion, the current population analysis confirms a number of findings previously described by conventional pharmacological analyses [6]. In particular, values for CL agreed with those reported previously, and BSA was a significant covariate as suggested by other population models with smaller numbers of patients [22, 23]. The current modeling efforts also, through the covariate analysis, have eliminated other candidate covariates from further consideration as important determinants of cisplatin disposition. It is difficult to make specific recommendations for dosing changes of cisplatin-containing chemotherapeutic regimens on the basis of the current findings. Although monitoring of unbound cisplatin plasma levels and dosage adjustment may be necessary to optimize cisplatin efficacy in cancer patients [31], therapeutic drug monitoring of cisplatin is not routinely available. Regardless, the described population pharmacokinetic model continues to increase our knowledge on this clinically important drug and provides the basis for designing future, prospective investigations aimed at refining the model and evaluating alternative and improved cisplatin dosing regimens.

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CHAPTER 6

Effect of administration vehicle on cisplatin disposition: plasma chloride concentration predicts unbound drug clearance

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Submitted

ABSTRACT

Purpose: To investigate the effect of two different cisplatin administration schedules on plasma pharmacokinetics and renal platinum excretion.

Experimental design: Ten patients were treated in a randomized intrapatient pharmacokinetic crossover study with cisplatin 50 mg/m^2 3-weekly as a 3-h infusion. Cisplatin was administered in 250 ml NaCl 3% with 1 l dextrose/saline prehydration and 3 l dextrose/saline posthydration (schedule 1), or in 85 ml NaCl 3% with 1.5 l dextrose/saline prehydration and 0.5 l dextrose/saline posthydration (schedule 2). Platinum concentrations in plasma and urine were determined by atomic absorption spectrometry.

Results: Compared to schedule 2, schedule 1 was associated with higher unbound platinum fraction at the end of cisplatin infusion (34.7 ± 6.21% versus 27.5 ± 7.00%, P = 0.009), slower plasma clearance of unbound platinum (26.6 ± 5.76 l/h versus 29.7 ± 8.38 l/h, P = 0.059) and higher cumulative renal platinum excretion (31.4 ± 2.85% versus 24.9 ± 6.75%, P = 0.046; n = 6). Plasma chloride concentrations at the end of infusion were higher with administration schedule 1 (106 ± 2.59 mmol/l versus 103 ± 1.92 mmol/l, P = 0.028), and inversely correlated with unbound platinum clearance (R^2 = 0.39, P = 0.008).

Conclusion: Administration of cisplatin in hypertonic saline influences cisplatin pharmacokinetics and urinary platinum excretion. It is hypothesized that chloride excess in the vehicle is associated with decreased formation of cisplatin hydrolysis products resulting in decreased protein binding and increased urinary excretion of unchanged cisplatin.

INTRODUCTION

Cis-diamminedichloroplatinum (cisplatin) is a commonly used anticancer drug with a broad spectrum of activity against malignant solid tumors [1]. Nausea, vomiting, renal dysfunction, neuropathy and hearing disturbances are important side effects; hematological toxicity is usually not a problem in conventional 3- or 4-weekly treatment regimens. Cisplatin-induced renal tubular toxicity is of major concern but can be substantially reduced by extensive hydration. Preclinical *in vivo* models have unequivocally demonstrated that the administration of cisplatin in a vehicle of hypertonic saline reduces renal toxicity [2, 3]. Clinical studies on high-dose or weekly dose-dense cisplatin have also suggested that administration in hypertonic saline yields less renal toxicity, but control groups were lacking [4-6]. Furthermore, pharmacokinetic studies on the effects of different hydration schedules and vehicles for cisplatin treatment in human cancer patients are sparse, and with conflicting results [5, 7, 8]. In the present analysis, we have prospectively assessed the influence of two commonly used cisplatin administration schedules with different volumes of hypertonic saline vehicle and hydration volumes on platinum plasma pharmacokinetics and urinary excretion.

PATIENTS AND METHODS

Study design and treatment schedules

The study design involved a prospective randomized crossover pharmacokinetic study. Treatment consisted of 3-weekly administration of cisplatin given intravenously at a dose of 50 mg/m^2 on day 1 followed by topotecan given intravenously at a dose of 0.75 mg/m^2 per day on days 1-5, which were the recommended doses from the phase I study by Rowinsky *et al*. [9]. Two different administration schedules for cisplatin were compared. In schedule 1, patients were treated with 1 l dextrose/saline prehydration over 3 h followed by a 3-h infusion of cisplatin dissolved in 250 ml of 3% (weight-to-volume ratio, w/v) sodium chloride (NaCl 3%) and posthydration with 3 l dextrose/saline over 12 h, as used in the phase I study on cisplatin/topotecan combination chemotherapy by De Jonge *et al*. [10]. In schedule 2, patients received 1.5 l dextrose/saline over 3 h followed by cisplatin dissolved in 85 ml NaCl 3% as a 3-h infusion, and posthydration with 0.5 l dextrose/saline over 30 min, as used by Rowinsky *et al*. [9]. Pre- and posthydration fluids contained potassium chloride (30 mmol/l) and magnesium sulfate (2 g/l). Before start of treatment, patients were randomized into two groups. Patients assigned to group A received schedule 1 during the first treatment course followed by schedule 2 during the second course; patients assigned to group B received the two treatment schedules in the reverse order. To avoid bias in cycle sequence and to keep the number of patients close for both treatment arms, a restricted randomization was applied by choosing a randomized block with use of a table of random numbers to create allocation sequence [11]. Antiemetic prophylaxis consisted of a $5HT_3$ antagonist in combination with dexamethasone. Diuretics were not routinely used. Topotecan was administered in 48 ml NaCl 0.9% over 30 min, immediately after cisplatin infusion on day 1. The administration of topotecan was repeated on days 2-5. No significant differences in topotecan pharmacokinetics between the two studied schedules were observed [12].

Patient eligibility

Patients were required to have a histologically or cytologically confirmed diagnosis of an advanced solid tumor for which there was no effective standard therapy, or for which combination therapy with cisplatin and topotecan was a reasonable treatment option. Age had to be 18-75 years, World Health Organization performance status 0-1, life expectancy > 12 weeks, hemoglobin ≥ 6.0 mmol/l, leukocytes ≥ 4.0 x 10^9/l, absolute neutrophil count ≥ 1.5 x 10^9/l, platelet count ≥ 100 x 10^9/l, bilirubin within normal limits, serum transaminases < 2 x the upper limit of normal (< 3 x the upper limit of normal in case of liver metastases), and creatinine clearance ≥ 60 ml/min. At least 4 weeks had to be lapsed since the last radiation therapy or chemotherapy (6 weeks for nitroseureas or mitomycin); no more than two prior chemotherapy regimens for metastatic disease were allowed. Other exclusion criteria were known or suspected brain and/or leptomeningeal

involvement and the presence of a contraindication against treatment with cisplatin and/or topotecan (such as significant cardiac disease, peripheral neuropathy ≥ grade 2, uncontrolled infection, pregnancy, breast feeding). Written informed consent was obtained before start of treatment. The study protocol was approved by the Medical Ethical Committee of Erasmus University Medical Center.

Pharmacokinetic analysis

Blood samples for measurement of platinum concentrations were drawn from the arm opposite to the infusion site and collected in 4.5-ml glass tubes containing lithium heparin as anticoagulant. Samples were collected immediately before cisplatin infusion, 1 and 2 h after the start of infusion, at the end of cisplatin infusion, and 0.5, 1, 2, 3 and 21 h after the end of cisplatin infusion. Immediately after sampling, plasma was separated by centrifugation at 3,000 x *g* for 10 min. Next, 500-µl aliquots of the plasma supernatant were added to 1.0 ml of ice-cold (-20°C) ethanol. After vortex mixing for 10 seconds, the ethanolic plasma samples were stored until the day of analysis. During the first 24 h from the start of cisplatin infusion, the excreted urine was collected in opaque containers and analyzed separately for the time intervals 0-12 h and 12-24 h after the start of cisplatin infusion. Plasma concentrations of total and unbound platinum, and platinum concentrations in urine were determined by flameless atomic absorption spectrometry as previously described [10]. In retrospect, plasma chloride concentrations were measured from plasma samples that had been obtained immediately before and at the end of cisplatin infusion.

Pharmacokinetic data were obtained by noncompartmental analysis using the software program WinNonLin (Version 4.0, Pharsight Corp., Mountain View, CA, USA). The area under the plasma concentration-time curve (AUC) of total platinum was calculated up to 24 h after the start of the cisplatin infusion, while the AUC of unbound platinum was calculated to infinity. Clearance (CL) was calculated by dividing the administered platinum dose by the observed AUC. Platinum excretion in the urine was expressed as percentage of administered dose.

Statistical analysis

Pharmacokinetic parameters are reported as mean ± standard deviation unless otherwise specified. For comparison of pharmacokinetic parameters between both treatment schedules, Wilcoxon's signed rank tests were applied with use of the software package SPSS (Version 9.0, SPSS Inc., Chicago, IL, USA). Correlations between pharmacokinetic parameters were examined by linear regression analysis, using the same program. Probability values of 0.05 or less were regarded as statistically significant.

RESULTS

A total of 13 patients was included in this pharmacokinetic study. Seven patients were assigned to treatment group A and 6 patients to treatment group B. Baseline patient characteristics are shown in Table 1. Two patients (no. 4 and 8) went off study after one treatment course due to gastrointestinal toxicity and renal impairment, respectively. Due to inadequate processing of blood samples, unbound platinum concentrations could not be measured during the first treatment course in another patient (no. 6). Thus, 10 patients (4 males and 6 females, evenly distributed over the treatment groups A and B) were assessable for cisplatin plasma pharmacokinetics; 6 of them (2 men and 4 women) were also assessable for urinary platinum excretion (in 4 patients urine collection was incomplete during at least one treatment course).

Table 1: Baseline patient characteristics

Patient no.	Gender	Age (years)	Tumor type	BSA (m^2)	Cisplatin dose (mg)
1	Female	60	Ovarian cancer	1.63	80
2	Female	39	Sarcoma	1.72	85
3	Male	60	SCLC	1.80	90
4	Female	58	ACUP	1.66	85
5	Female	43	Gastric cancer	1.68	85
6	Male	54	Acinic cell carcinoma	1.86	95
7	Female	66	ACUP	1.70	85
8	Female	46	Salivary gland carcinoma	1.53	80
9	Male	36	ACUP	1.81	95
10	Female	43	Cervical cancer	1.53	80
11	Female	68	Vulva carcinoma	2.07	100
12	Male	54	Head/neck cancer	1.95	100
13	Male	43	Head/neck cancer	1.86	90

SCLC, small-cell lung cancer; ACUP, adenocarcinoma of unknown primary site; BSA, body-surface area

Results on platinum pharmacokinetics are summarized in Table 2. Peak plasma concentrations of total and unbound platinum did not significantly differ between schedules 1 and 2. At the end of cisplatin infusion, the unbound platinum fraction was higher in schedule 1, compared to schedule 2 (34.7 ± 6.21% versus 27.5 ± 7.00%, P = 0.009). A positive correlation was observed between the unbound platinum fraction at the end of infusion and the AUC of unbound platinum (R^2 = 0.77, P < 0.001). Unbound platinum CL was slightly slower in schedule 1 (26.6 ± 5.76 l/h versus 29.7 ± 8.38 l/h, P = 0.059), whereas total platinum CL was similar for both administration schedules.

Plasma chloride concentrations at the end of cisplatin infusion were significantly higher after administration in 250 ml compared to 85 ml NaCl 3% (106 ± 2.59 versus 103 ± 1.92 mmol/l, P = 0.028); plasma chloride levels determined just before start of infusion were not

Table 2: Cisplatin plasma pharmacokinetics and urinary platinum excretion

		Schedule 1[a]	Schedule 2[b]	
$C_{max, total}$	(µg/ml)	2.01 ± 0.220	1.96 ± 0.294	$P = 0.54$
$C_{max, unbound}$	(µg/ml)	0.768 ± 0.140	0.704 ± 0.197	$P = 0.24$
CL_{total}	(l/h)	1.94 ± 0.304	1.95 ± 0.383	$P = 0.95$
$CL_{unbound}$	(l/h)	26.6 ± 5.76	29.7 ± 8.38	$P = 0.059$
$T_{1/2, total}$	(h)	44.4 ± 12.2	44.9 ± 12.0	$P = 0.72$
$T_{1/2, unbound}$	(h)	0.752 ± 0.219	0.739 ± 0.174	$P = 0.80$
$AUC_{unbound} : AUC_{total}$		0.0746 ± 0.0128	0.0689 ± 0.0201	$P = 0.24$
$F_{unbound, end\ of\ infusion}$	(%)	34.7 ± 6.21	27.5 ± 7.00	$P = 0.009$
Pt excreted, 0-24 h	(%)	31.4 ± 2.85	24.9 ± 6.75	$P = 0.046$

$C_{max, total}$, maximal plasma concentration of total platinum; $C_{max, unbound}$, maximal plasma concentration of unbound platinum; CL_{total}, plasma clearance of total platinum; $CL_{unbound}$, plasma clearance of unbound platinum; $T_{1/2, total}$, plasma half-life of total platinum; $T_{1/2, unbound}$, plasma half-life of unbound platinum; $AUC_{unbound}$, area under the plasma concentration-time curve of unbound platinum; AUC_{total}, area under the plasma concentration-time curve of total platinum; $F_{unbound, end\ of\ infusion}$, unbound platinum fraction at the end of cisplatin infusion expressed as percentage of total platinum concentration in plasma; Pt excreted, 0-24 h, amount of platinum excreted into the urine during the first 24 hours from the start of cisplatin infusion expressed as percentage of the amount of platinum administered.

[a]Schedule 1 = Cisplatin administered in 250 ml NaCl 3% as a 3-h infusion with 1 l dextrose/saline prehydration over 3 h and 3 l dextrose/saline posthydration over 12 h.
[b]Schedule 2 = Cisplatin administered in 85 ml NaCl 3% as a 3-h infusion with 1.5 l dextrose/saline prehydration over 3 h and 0.5 l dextrose/saline posthydration over 30 min.

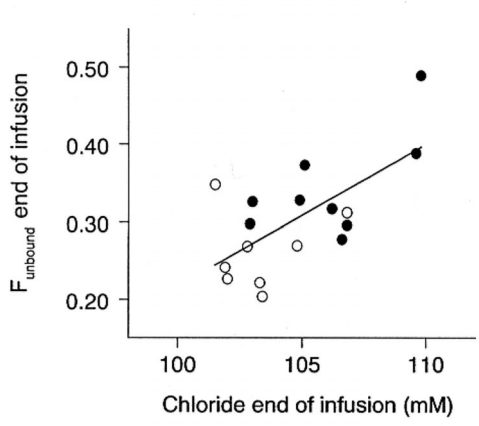

Figure 1
Unbound platinum fraction at the end of cisplatin infusion ($F_{unbound\ end\ of\ infusion}$) *versus* plasma chloride concentration at the end of cisplatin infusion: $R^2 = 0.43$ ($P = 0.004$). Closed circles represent treatment schedule 1 (cisplatin administered in 250 ml NaCl 3%); open circles represent treatment schedule 2 (cisplatin administered in 85 ml NaCl 3%)

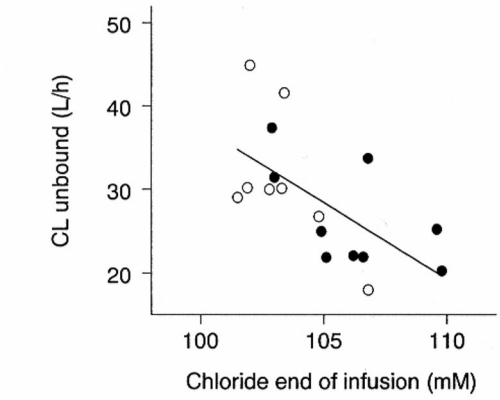

Figure 2
Plasma clearance of unbound platinum ($CL_{unbound}$) *versus* plasma chloride concentration at the end of cisplatin infusion: R^2 = 0.39 (P = 0.008). Closed circles represent treatment schedule 1 (cisplatin administered in 250 ml NaCl 3%); open circles represent treatment schedule 2 (cisplatin administered in 85 ml NaCl 3%)

significantly different between both administration schedules. Plasma chloride concentration and unbound platinum fraction at the end of infusion were clearly correlated (R^2 = 0.43, P = 0.004), as shown in Figure 1. Unbound platinum CL inversely correlated with the plasma chloride concentration at the end of cispatin infusion (R^2 = 0.39, P = 0.008), which is illustrated in Figure 2.

The 24-h urine output was 4342 ± 909 ml with schedule 1 and 3752 ± 541 ml with schedule 2 (P = 0.075). During the first 12 h after start of the cisplatin infusion, no significant difference (P = 0.46) in urine output was observed, but during the period 12-24 h after start of the cisplatin infusion, the urine output was 1792 ± 433 ml with schedule 1 and only 949 ± 420 ml with schedule 2 (P = 0.027). This was accompanied with higher urinary platinum concentration in the period 12-24 h after start of cisplatin with use of administration schedule 2 (2.52 ± 1.56 µg/ml versus 0.93 ± 0.16 µg/ml; P = 0.028), whereas no significant difference was observed during the first 12 h (4.47 ± 1.39 µg/ml versus 6.89 ± 2.27 µg/ml; P = 0.18). With the use of administration schedule 1, 31.4 ± 2.85% was excreted in the urine after 24 h compared with 24.9 ± 6.75% with the use of schedule 2 (P = 0.046).

DISCUSSION

The present study indicates that the administration of hypertonic saline vehicle influences cisplatin pharmacokinetics. At the end of a 3-h cisplatin infusion, the unbound platinum fraction was significantly higher after administration in 250 ml NaCl 3% than after administration in 85 ml NaCl 3%. The difference in urinary platinum excretion between both administration schedules can probably be explained by the observed difference in unbound platinum fraction, along with the rapid clearance of unbound cisplatin by the kidneys [13]. Overall, the plasma CL of unbound platinum was slightly slower after the administration of cisplatin in 250 ml NaCl 3% than after administration in 85 ml NaCl 3%, which is probably the resultant of decreased protein binding, partly opposed by increased renal excretion of platinum.

It has already been hypothesized that chloride ions counteract cisplatin aquation reactions resulting in decreased formation of highly reactive platinum hydrolysis products along with decreased protein binding [2, 14]. At the end of cisplatin infusion, plasma chloride levels were significantly higher after administration in 250 ml NaCl 3% than after administration in 85 ml NaCl 3%. It is also noteworthy that plasma chloride concentration and unbound platinum fraction at the end of infusion were clearly correlated (Figure 1); unbound platinum CL was inversely correlated with the plasma chloride concentration at the end of cispatin infusion (Figure 2).

In the present study, two different pre- and posthydration schedules were used, but it is unlikely that this had significant influence on plasma pharmacokinetics and overall urinary platinum excretion. The difference in prehydration schedules was minor, certainly in comparison to the difference between vehicles. Posthydration schedules were more different between both treatment schedules. However, the crucial phase regarding unbound platinum kinetics is during cisplatin infusion and few hours thereafter, and during this period both posthydration schedules were comparable. Urine output during the first 12 h after the start of cisplatin infusion did not differ between both treatment schedules. The posthydration schedule was also not likely to influence overall urinary platinum excretion; > 85% of all platinum excreted after 24 h was excreted during the first 12 h after start of the cisplatin infusion.

In view of our observations, amelioration of renal toxicity after administration of cisplatin in hypertonic saline is not mediated through decreased urinary platinum excretion, as has been suggested by Dumas *et al*. [8]. Another study found no significant differences in urinary platinum excretion using NaCl 3% or NaCl 0.9% as the vehicle for cisplatin administration [7]. Recent data from a phase I study* on the novel farnesyltransferase inhibitor BMS-214662 followed by cisplatin 75 mg/m^2 as a 4-h infusion, showing significantly increased 24-h urinary platinum excretion after administration of cisplatin in 250 ml NaCl 3% compared with cisplatin administration in 1 l NaCl 0.9%, are more in line with the results of the present study. The reason for the discordance between these studies is not clear, but is probably related to differences in cisplatin dose, infusion rate, and administration schedule.

With regard to renal toxicity, not only the absolute platinum exposure but also the composition of platinum species to which the kidneys are exposed, is relevant. Hydrolysis products of cisplatin are approximately three times more nephrotoxic than cisplatin itself [15]; forced chloruresis may prevent the formation of these hydrolysis products inside the renal tubule leading to reduction of renal tubular toxicity [5, 16]. Besides the supposed beneficial effect of chloride excess in the vehicle, there is also the possibility of a protective effect from the sodium in the hypertonic saline vehicle. Recently, an *in vitro* study showed that in cell cultures, rather small changes in sodium ion concentrations inside the medium resulted in substantial differences in the toxic effects of cisplatin toward renal tubular cells but not toward tumor cells [17]; the clinical value of this observation, however, remains to be determined.

Whether differences in pharmacokinetic behavior related to administration in hypertonic saline also influence antitumor activity of cisplatin is a matter of concern.

Animal studies yielded conflicting results [2, 16, 18], whereas appropriate clinical studies on this issue are lacking. Thus, additional clinical research on the consequences of the administration of cisplatin in hypertonic saline on antitumor efficacy is required.

In conclusion, the composition of the vehicle for cisplatin infusion has influence on platinum pharmacokinetics. Administration of cisplatin in 250 ml versus 85 ml hypertonic saline was associated with an increase in the unbound fraction of platinum in the plasma and an increase in the amount of platinum excreted in the urine. This is probably related to decreased protein binding through an excess of chloride ions provided by the vehicle. Furthermore, correlations were found between plasma chloride concentration and pharmacokinetic parameters such as unbound platinum fraction, urinary platinum excretion and unbound platinum clearance, suggesting that plasma chloride concentration could have predictive value toward cisplatin pharmacokinetics.

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CHAPTER 7

Summary and conclusions

The present thesis includes clinical and pharmacological studies on cisplatin dosing and scheduling. Cisplatin is a cytotoxic anticancer drug with a broad spectrum of antineoplastic activity, and is widely used in the treatment of germ cell, ovarian, endometrial, cervical, urothelial, head/neck and lung cancer. Conventional use consists of the 3-or 4-weekly intravenous administration of a body-surface area (BSA) adjusted dose (usually 50-100 mg/m^2) of cisplatin along with vigorous intravenous hydration in order to minimalize the risk of cisplatin-induced renal toxicity. Based on results in animal studies, it was postulated that the administration of cisplatin in hypertonic saline might result in additional protection against renal toxicity. Indeed, Ozols *et al*. demonstrated that, using a vehicle of hypertonic saline, high-dose cisplatin treatment (200 mg/m^2 in 5 daily divided doses every 4 weeks) was tolerated without an excess of nephrotoxicity. Furthermore, Planting *et al*. showed the feasibility of dose-dense treatment consisting of cisplatin 70-80 mg/m^2 weekly administered in hypertonic saline (chapter 1).

On theoretical grounds, increasing cisplatin dose-intensity could result in enhanced antitumor efficacy; shortening the treatment interval (dose-dense therapy) may reduce the time for recovery and regrowth of tumor cells between treatment courses. Combination chemotherapy (preferably using drugs with synergistic antitumor effects and nonoverlapping toxicity) is another approach to improve the efficacy of anticancer treatment. In the treatment of ovarian cancer, platins (cisplatin or carboplatin) are the most active class of anticancer drugs and form the backbone of anticancer drug treatment. Paclitaxel also exerts significant antitumor activity in this disease. From this perspective, combination of dose-dense cisplatin with paclitaxel could be an attractive therapeutic option for patients with ovarian cancer. Therefore, we conducted a randomized phase I/II trial with dose-dense cisplatin (70 mg/m^2 on days 1, 8, 15, 29, 36, and 43) in combination with escalating doses of paclitaxel either 4-weekly or weekly in patients with advanced ovarian cancer (chapter 2) to determine the feasibility and estimate response rates. A total of 49 patients were entered onto this trial. Paclitaxel could safely be escalated to 225 mg/m^2 4-weekly or 100 mg/m^2 weekly, with fatigue as major adverse event. Myelosuppression, renal toxicity and neurotoxicity were only mild to moderate. No pharmacokinetic interaction was found between paclitaxel and cisplatin, whereas there was a two-fold reduction of cisplatin-DNA adduct formation in leukocytes as compared with cisplatin administered without paclitaxel. Patients in this study were either chemotherapy-naïve or had a first relapse after platinum-based chemotherapy. After (re-) induction with the above-mentioned weekly cisplatin regimen, 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 was 17 months (23 months in chemotherapy-naïve patients; 11 months in patients having received prior platinum-based chemotherapy). Median overall survival was 41 months (48 months in chemotherapy-naïve patients; 24 months in patients having received prior platinum-based chemotherapy). From this study, it was concluded that weekly cisplatin in combination with paclitaxel either weekly or 4-

weekly paclitaxel had notable antitumor activity with manageable toxicity in patients with advanced ovarian cancer.

In order to obtain more insight into the feasibility and prognostic indicators for toxicity of weekly high-dose (70-85 mg/m^2) cisplatin, we performed a large retrospective study in 400 patients (203 men, 197 women; median age 54 years) receiving this treatment in the period 1990-2001. As described in chapter 3, most patients took part in phase I/II trials assessing the feasibility and efficacy of weekly cisplatin alone, or in combination with paclitaxel or etoposide. Cisplatin was administered in 250 ml NaCl 3% over 3 hours, for six intended administrations. The mean number of administrations was 5.3 (range, 1-6). Anemia was a common side effect. A total of 202 patients (51%) received one or more transfusions; the median number of erythrocyte units transfused was 2 (range, 0-17). Febrile neutropenia occurred in 1.5% of patients. Nadir platelet count < 50 x 10^9/L was observed in 22% of the patients who received at least three administrations of weekly cisplatin; 19 patients (5%) received platelet transfusions. Nephrotoxicity defined as a ≥ 25% reduction in creatinine clearance was observed in 116 patients (29%). Neurotoxicity and ototoxicity developed or worsened in 188 patients (47%) and 168 patients (42%) respectively, and was mild to moderate in the vast majority of cases. Reasons not to complete the six treatment cycles were disease progression (7.5%), hematological toxicity (9%), nephrotoxicity (7%), ototoxicity (2.5%), neurotoxicity (1%), gastrointestinal toxicity (1%), cardiovascular complications (0.5%) or combination of reasons including noncompliance and patient's request (5.5%). Logistic regression analysis was used to evaluate baseline parameters for prognostic value regarding toxicity. Leukopenia correlated with etoposide cotreatment, and thrombocytopenia with cisplatin dose and prior (platinum-based) chemotherapy. Risk factors for nephrotoxicity were increasing age, female gender, smoking, hypoalbuminemia and paclitaxel coadministration. Neurotoxicity grade 2-4 (observed in 11% of the patients) was associated with prior chemotherapy and paclitaxel coadministration, while anemia at baseline was predisposing for symptomatic hearing loss (observed in 15% of patients). From this study, it was concluded that, also when combined with oral etoposide or intravenous paclitaxel, weekly high-dose cisplatin administered in hypertonic saline is a feasible treatment regimen. Predisposing factors for treatment-related toxicity differed from side effect to side effect.

In addition to the above-mentioned studies with an emphasis on the pharmacodynamic aspects of cisplatin chemotherapy, this thesis also includes investigations on cisplatin pharmacokinetics. In chapter 4, we report a pharmacokinetic study in 268 cancer patients (163 men and 105 women) with a median age of 54 years (range, 21-74 years) who were treated in phase I/II trials with cisplatin monotherapy or combination chemotherapy with etoposide, irinotecan, topotecan, or docetaxel. Cisplatin was administered as a 3-hour infusion either weekly (93 patients) or once every 3 weeks (175 patients) at dose levels of 50-100 mg/m^2. Analysis of 485 complete treatment courses was based on measurement of total and non-protein-bound cisplatin in plasma by atomic absorption spectrometry. No pharmacokinetic interaction was found between cisplatin and the anticancer drugs used in combination therapies. The mean plasma clearance of unbound cisplatin was 57.1 ±

14.7 l/h (range, 31.0-116 l/h) with an interpatient variability of 25.6% and an intrapatient variability of 12.1%. As for most other anticancer drugs, cisplatin dosing is based on BSA with the aim of reducing interindividual variability of drug effects. In this study, the relevance of this concept for cisplatin was evaluated. BSA varied between 1.43 and 2.40 m^2 (mean, 1.86 ± 0.19 m^2) with an interpatient variability of 10.4%. When unbound platinum clearance was corrected for BSA, the interindividual variability remained in the same order (23.6% versus 25.6%). Furthermore, only a weak correlation was found between unbound platinum clearance and BSA ($r = 0.42$). It was concluded that in view of the high interpatient variability in unbound platinum clearance relative to the variation in observed BSA, there is no rationale for BSA-based dosing of cisplatin. This is not surprising if one considers the rather complex pharmacological behavior of cisplatin, which includes several processes that are unlikely to be dependent on BSA. For example, during and shortly after intravenous administration of cisplatin rapid renal excretion of unbound cisplatin takes place at a clearance rate much higher than the glomerular filtration rate, suggesting that unbound cisplatin is excreted by the kidneys through an active tubular secretion process. Furthermore, only 20 to 35% of the administered dose can be retrieved in the urine during and after drug administration, which can be explained by progressive, strong and partially irreversible binding to plasma proteins (mainly albumin). Binding to cellular proteins and nucleic acids also occurs.

For these reasons, we evaluated a number of patient variables (age, sex, hematocrit, total protein, albumin, serum creatinine, creatinine clearance) in addition to common measures of body size (i.e. height, weight, BSA) on their influence on cisplatin pharmacokinetics in a nonlinear mixed-effect model (chapter 5). Data were obtained from 285 patients (519 treatment cycles; 4643 plasma samples) who received the drug as a 3-hour intravenous infusion at a mean dose of 144 mg (range, 75-210 mg). A NONMEM population model was built by performing generalized additive modeling to identify candidate covariates. The final models for unbound cisplatin clearance and volume of distribution were obtained using a backward deletion protocol. The final model was a 1-compartment linear model with yet BSA as the only significant covariate that impacted on both unbound cisplatin clearance and volume of distribution. It was concluded that, in the patient population studied, cisplatin pharmacokinetics was not associated with age, sex, hematocrit, plasma levels of total protein and albumin, and measures of renal function.

In each study described in chapters 2, 3, 4, and 5, cisplatin was administered in 250 ml of NaCl 3%. The rationale behind the administration of cisplatin in hypertonic saline is to create an excess of chloride ions, which forces the equilibrium between chlorinated and hydrated platinum species into the direction of the less nephrotoxic chlorinated form. Although the validity of this concept was proved in experimental animal-models, knowledge on the relation between the administration vehicle and cisplatin pharmacokinetics in human cancer patients is lacking. In chapter 6, we describe the results of a randomized intrapatient pharmacokinetic crossover study in 10 evaluable patients who were treated with cisplatin 50 mg/m^2 3-weekly as a 3-hour infusion. Cisplatin was dissolved either in 250 ml NaCl 3%, or in 85 ml NaCl 3%. Patients assigned to receive

cisplatin in 250 ml NaCl 3% during the first treatment course received cisplatin in 85 ml NaCl 3% during the second course, and vice versa. Platinum concentrations in plasma and urine were determined by atomic absorption spectrometry. Compared with cisplatin administration in 85 ml NaCl 3%, administration in 250 ml NaCl 3% was associated with higher unbound platinum fraction at the end of cisplatin infusion, slower plasma clearance of unbound platinum and higher cumulative renal platinum excretion. Plasma chloride concentrations at the end infusion were significantly higher after administration in 250 ml NaCl 3% than after administration in 85 ml NaCl 3%. Furthermore, plasma chloride concentration and unbound platinum fraction at end of infusion were clearly correlated (R^2 = 0.43, P = 0.004). Plasma chloride concentration at end of infusion inversely correlated with unbound platinum clearance (R^2 = 0.39, P = 0.008). We concluded that the vehicle of administration influences cisplatin pharmacokinetics and urinary platinum excretion. The most likely explanation is that chloride excess in the vehicle is associated with decreased formation of cisplatin hydrolysis products resulting in decreased protein binding and increased urinary excretion of unchanged cisplatin.

FINAL CONCLUSIONS AND PERSPECTIVES

Cisplatin is known as an anticancer agent with substantial toxicity. Nevertheless, dose-dense treatment at a weekly dose of 70-80 mg/m^2 administered in a vehicle of hypertonic saline is feasible. Furthermore, we demonstrated that cisplatin 70 mg/m^2 weekly could be combined with paclitaxel either 4-weekly or weekly, yielding excellent antitumor activity in patients with advanced ovarian cancer, including in patients with disease progression during or after conventional platinum-based chemotherapy. Provided that contraindications against cisplatin-based chemotherapy are absent, weekly dose-dense cisplatin chemotherapy can be considered in the treatment of patients with platinum-resistant or platinum-refractory ovarian cancer. Weekly dose-dense cisplatin treatment may also be combined with either intravenous paclitaxel or oral etoposide. The potential of dose-dense cisplatin chemotherapy in other tumor types than ovarian cancer remains to be determined.

Risk factors for nephrotoxicity resulting from weekly cisplatin treatment are increasing age, female gender, cigarette smoking, hypoalbuminemia and paclitaxel cotreatment. Neurotoxicity is associated with prior (platinum-based) chemotherapy and paclitaxel cotreatment, and hearing loss with anemia at baseline. None of these risk factors, however, are to be considered absolute contraindications for dose-dense cisplatin chemotherapy.

Cisplatin dose is usually guided by the patient's BSA. However, we found that the correlation between unbound cisplatin clearance and BSA is too weak to warrant the routine use of BSA-based dosing. Alternative patient-related factors such as age, sex, hematocrit, total protein, albumin and creatinine clearance were found to have even less impact on unbound cisplatin clearance and volume of distribution, as demonstrated by the

development of a NONMEM population pharmacokinetic model. In a relatively small pharmacokinetic intrapatient crossover study comparing two commonly used cisplatin administration schedules, interesting associations between plasma chloride concentration and unbound cisplatin fraction at the end of cisplatin infusion, and between plasma chloride concentration and unbound platinum clearance were found. Whether plasma chloride concentrations can predict cisplatin-induced toxicity or antitumor activity needs further study. The present results indicate that there is no rationale for any dose-individualization strategy with regard to cisplatin treatment. Unless better predictors for unbound cisplatin clearance are identified, we recommend fixed-dosing regimens for cisplatin in adult cancer patients. Considering the therapeutic dose range of 50-100 mg/m^2 and the BSA of 1.86 ± 0.19 m^2 in our patient population, in patients with BSA between 1.6 and 2.1 m^2, a fixed dose can be used as indicated in the following table:

Cisplatin dose in mg per m^2 BSA	Fixed cisplatin dose in mg for all patients
50	95
60	110
70	130
75	140
80	150
100	185

Whether this also applies to patients at the extremes of BSA is the subject of an ongoing prospective pharmacokinetic study.

CHAPTER 7

Samenvatting en conclusies

In dit proefschrift worden de resultaten besproken van een aantal onderzoeken betreffende dosering en wijze van toediening van het antikanker geneesmiddel cisplatine. Cisplatine heeft een breed indicatiegebied en wordt onder andere gebruikt bij de behandeling van kanker uitgaande van teelbal, eierstok, baarmoeder, urinewegen, blaas, long en hoofd/halsregio. De gebruikelijke behandeling bestaat uit intraveneuze toediening van een dosis cisplatine die berekend wordt op geleide van het lichaamsoppervlak van de patiënt (meestal 70-100 mg/m^2) in een frequentie van eenmaal per 3 of 4 weken. Rondom de toediening van cisplatine wordt 2-6 liter extra vocht per infuus toegediend om nierschade tegen te gaan. Onderzoek bij proefdieren (vooral muizen en ratten) heeft laten zien dat toediening van cisplatine in een hypertone oplossing van keukenzout (natriumchloride, NaCl) de kans op nierschade nog aanzienlijk verder kan beperken. Uit eerder onderzoek bij mensen met kanker is gebleken dat door toediening in hypertoon zout de dosis cisplatine kan worden verdubbeld naar 200 mg/m^2 (verdeeld over 5 achtereenvolgende dagen). Tevens bleek het mogelijk cisplatine opgelost in hypertoon zout wekelijks toe te dienen in een dosis van 70-80 mg/m^2 (hoofdstuk 1).

Op theoretische gronden zal verhoging van de dosisintensiteit kunnen leiden tot een toegenomen antitumor effectiviteit; verkorting van het dosisinterval geeft de tumorcellen minder gelegenheid tot herstel en uitgroei tussen de chemotherapiekuren door. Een andere strategie om de effectiviteit van de behandeling van kanker te verhogen, is combinatietherapie met één of meer andere antikanker geneesmiddelen. In de hieronder beschreven studies is cisplatine dan ook meestal onderzocht in combinatie met andere geneesmiddelen. In hoofdstuk 2 wordt een fase I/II onderzoek beschreven, waarbij patiënten met eierstokkanker werden behandeld met een dosisintensief schema bestaande uit cisplatine 70 mg/m^2 in 250 ml NaCl 3% op dag 1, 8, 15, 29, 36 en 43, in combinatie met paclitaxel in een dosering van 60, 70, 80, 90 of 100 mg/m^2 wekelijks, ofwel 135, 150, 175, 200 of 225 mg/m^2 eenmaal per 4 weken. Belangrijkste doelen van dit onderzoek waren bepaling van de klinische toepasbaarheid en inschatting van de responspercentages. In totaal namen 49 patiënten deel aan dit onderzoek. Ondanks toepassing van het dosisintensieve cisplatineschema kon de dosis paclitaxel worden verhoogd tot 100 mg/m^2 per week of 225 mg/m^2 per 4 weken. Bij de hoogste doseringen paclitaxel was moeheid de belangrijkste bijwerking. Bijwerkingen met betrekking tot bloedaanmaak, nierfunctie en zenuwstelsel waren beperkt. Farmacokinetisch onderzoek toonde in het plasma geen interactie tussen paclitaxel en cisplatine. Wel werd ten opzichte van behandeling met cisplatine zonder paclitaxel een halvering gezien van het aantal DNA-platina adducten in de witte bloedcellen, hetgeen de verklaring zou kunnen zijn voor het feit dat paclitaxel kon worden toegevoegd aan dosisintensieve cisplatinebehandeling zonder dosisbeperkende leukocytopenie. In totaal waren 42 van de 49 patiënten evalueerbaar voor respons; bij 4 patiënten was sprake van adjuvante behandeling na optimale chirurgische behandeling zonder aantoonbare tumorrest en 3 patiënten voltooiden de inductiechemotherapie niet vanwege bijwerkingen. Een objectieve tumorrespons werd vastgesteld bij 16 van de 17 evalueerbare patiënten (94%) die niet eerder met chemotherapie waren behandeld en bij 21 van de 25 patiënten (84%) met

ziekteprogressie tijdens of na conventionele eerstelijns platinum (cisplatine of carboplatin) bevattende chemotherapie. De mediane progressievrije overleving bedroeg 17 maanden (23 maanden bij niet chemotherapeutisch voorbehandelde en 11 maanden bij chemotherapeutisch voorbehandelde patiënten). De mediane overleving was 41 maanden (48 maanden bij niet chemotherapeutisch voorbehandelde en 24 maanden bij chemotherapeutisch voorbehandelde patiënten). Wekelijkse, dosisintensieve behandeling met cisplatine in combinatie met paclitaxel wekelijks of eenmaal per 4 weken is derhalve bij (recidief) eierstokkanker een zeer effectief chemotherapieschema met aanvaardbare bijwerkingen.

Teneinde een beter inzicht te krijgen in het bijwerkingenprofiel van wekelijkse, dosisintensieve behandeling met cisplatine werd een retrospectief onderzoek verricht bij 400 patiënten (203 mannen en 197 vrouwen) met een mediane leeftijd van 54 jaar die waren behandeld in de periode 1990-2001 (hoofdstuk 3). Het merendeel van deze patiënten was in onderzoeksverband behandeld met cisplatine monotherapie, dan wel in combinatie met paclitaxel of etoposide. De geplande behandeling bestond telkens uit 6 toedieningen van cisplatine in een dosis van 70-85 mg/m^2, opgelost in 250 ml NaCl 3%, als 3-uurs infuus. Gemiddeld werden 5,3 cisplatinekuren toegediend; 263 patiënten (66%) kregen 6 kuren. Redenen de behandeling eerder af te breken waren tumorprogressie (bij 7,5% van de patiënten), hematologische toxiciteit (9%), nierfunctieproblemen (7%), gehoorsschade (2,5%), zenuwschade (1%), maag/darmproblemen (1%), cardiovasculaire complicaties (0,5%) of andere redenen waaronder een gebrek aan therapietrouw (5,5%). Eén van de meest frequent optredende bijwerkingen was bloedarmoede. Bij de helft van de patiënten werd de behandeling ondersteund door bloedtransfusies (mediaan 2 eenheden erythrocytenconcentraat). Neutropene koorts trad op bij slechts 1,5% van de patiënten. Een daling van het aantal bloedplaatjes beneden 50 x 10^9/l werd gezien bij 22% van de patiënten die tenminste 3 cisplatinekuren kregen toegediend; 19 patiënten (5%) werden behandeld met bloedplaatjestransfusies. Een nierfunctiestoornis (minimaal 25% afname van de creatinineklaring) trad op bij 116 patiënten (29%). Bijwerkingen met betrekking tot het zenuwstelsel of gehoorsorgaan werden gevonden bij respectievelijk 188 patiënten (47%) en 168 patiënten (42%); meestal waren deze bijwerkingen betrekkelijk mild. Onderdeel van het onderzoek was tevens een logistische regressieanalyse naar voorspellende factoren ten aanzien van de verschillende bijwerkingen van wekelijkse, dosisintensieve behandeling met cisplatine. Combinatie met etoposide was gerelateerd aan de mate van daling van het aantal witte bloedcellen. Daling van het aantal bloedplaatjes beneden 50 x 10^9/l was gecorreleerd met de dosis cisplatine en eerdere behandeling met platinum bevattende chemotherapie. Hogere leeftijd, vrouwelijk geslacht, roken, een verlaagd serum albuminegehalte en gelijktijdige behandeling met paclitaxel waren onafhankelijke risicofactoren voor het optreden van nierfunctiestoornissen. Bijwerkingen met betrekking tot het zenuwstelsel waren geassocieerd met eerdere (platinum bevattende) chemotherapie en gelijktijdige behandeling met paclitaxel; bloedarmoede predisponeerde voor symptomatisch gehoorsverlies. Geconcludeerd werd dat wekelijkse, dosisintensieve cisplatine chemotherapie toepasbaar is, en dat

risicofactoren ten aanzien van de diverse bijwerkingen verschillen.

Naast bovengenoemde onderzoeken, waarin de nadruk ligt op de farmacodynamische aspecten van wekelijkse, dosisintensieve cisplatinebehandeling, vormen ook farmacokinetische studies een belangrijk onderdeel van dit proefschrift. In hoofdstuk 4 wordt een onderzoek beschreven bij 268 patiënten met kanker die in fase I/II studieverband werden behandeld met cisplatine als monotherapie, dan wel gecombineerd met etoposide, irinotecan, topotecan of docetaxel. Het betrof 163 mannen en 105 vrouwen in de leeftijd van 21-74 (mediaan: 54) jaar. Cisplatine werd toegediend als 3-uurs infuus in een dosis van 50-100 mg/m^2, eenmaal per 3 weken (175 patiënten) of wekelijks (93 patiënten). Van 485 kuren werd het beloop in de tijd van de platinaconcentraties in bloedplasma geanalyseerd met behulp van atomaire absorptie spectrometrie. Farmacokinetische interacties tussen cisplatine en de andere antikanker geneesmiddelen werden niet gevonden. De plasmaklaring van het niet aan eiwit gebonden (= vrij) platina varieerde tussen 31,0 en 116 l/h (gemiddeld 57,1 ± 14,7 l/h) met een interindividuele variatie van 25,6% en een intrapatiënt variatie van 12,1%. Het lichaamsoppervlak (body-surface area, BSA) van de patiënten was 1,43-2,40 m^2 (gemiddeld 1,86 ± 0,19 m^2) met een interindividuele variatie van 10,4%. Correctie voor BSA leidde niet tot een belangrijke vermindering van de interindividuele variatie in de plasmaklaring van vrij cisplatine (23,6% versus 25,6%). Bovendien was de correlatie tussen klaring en BSA te gering (r = 0,42) om de routinematig toegepaste methode van dosisindividualisatie op grond van BSA te kunnen ondersteunen. Dit is te verklaren doordat de farmacokinetische processen die een rol spelen bij de klaring van cisplatine (binding aan eiwitten; glomerulaire filtratie en vooral tubulaire excretie via de nieren) grotendeels onafhankelijk van BSA zijn. Derhalve werd vervolgens onderzoek verricht naar de relatie tussen een aantal patiëntgebonden variabelen (leeftijd, geslacht, lengte, gewicht, BSA, hematocriet, serumconcentraties totaal eiwit, albumine en creatinine, creatinineklaring) en de farmacokinetiek van cisplatine (hoofdstuk 5). Gegevens werden verzameld van 519 cisplatinekuren (in totaal 4643 plasmamonsters) bij in totaal 285 patiënten die waren behandeld met cisplatine als 3-uurs infuus in een dosis van 75-210 mg (gemiddeld 144 mg). Een NONMEM populatiemodel werd in 3 stappen opgebouwd. In eerste instantie werd een model zonder covariaten geconstrueerd. Vervolgens werden met behulp van GAM ('generalized additive modeling') potentiële covariaten geselecteerd die van invloed zouden kunnen zijn op de farmacokinetiek. Tenslotte werd het definitieve computermodel voor plasmaklaring en verdelingsvolume van vrij platina opgebouwd: een lineair 1-compartimentsmodel met BSA als enige significante factor. Teleurstellend was dat geen van de andere onderzochte patiëntgebonden variabelen in staat was de interindividuele variatie in de farmacokinetiek van cisplatine te verminderen, terwijl ook in dit onderzoek de relatie tussen cisplatineklaring en BSA onvoldoende sterk was voor routinematige dosisindividualisatie op geleide van BSA.

In de onderzoeken beschreven in hoofdstuk 2, 3, 4 en 5 werd cisplatine toegediend in 250 ml NaCl 3%. Uitgangspunt voor de toediening van cisplatine in een oplossing van hypertoon zout is het aanbieden van een overmaat aan chloride ionen, zodat het

evenwicht tussen gechloreerde en gehydrateerde platinaverbindingen verschuift in de richting van de gechloreerde platinaverbindingen die met name voor de nieren minder schadelijk zijn. Ondanks het feit dat de juistheid van dit concept overtuigend is aangetoond in proefdieren, is bij mensen met kanker weinig bekend over de farmacokinetiek van cisplatine toegediend in hypertoon zout. In hoofdstuk 6 wordt een farmacokinetisch onderzoek besproken bij patiënten met kanker die werden behandeld met cisplatine in een dosis van 50 mg/m^2 als 3-uurs infuus eenmaal per 3 weken. Patiënten werden gerandomiseerd tussen twee verschillende cisplatine toedieningschema's: bij schema 1 werd cisplatine toegediend in 250 ml NaCl 3% en bij schema 2 in 85 ml NaCl 3%. Patiënten die de eerste kuur volgens schema 1 werden behandeld, kregen de tweede kuur volgens schema 2, en andersom. Plasmamonsters werden afgenomen vlak voor cisplatinetoediening, 1 en 2 uur na starten van het cisplatine-infuus, aan het eind van de toediening en 1/2, 1, 2, 3 en 21 uur na afloop van het cisplatine-infuus. Tevens werd gedurende 24 uur urine verzameld. Platinaconcentraties in plasma en urine werden bepaald met behulp van atomaire absorptie spectrometrie. Er waren 10 patiënten evalueerbaar voor plasmakinetiek en 6 voor urinekinetiek. Toediening van cisplatine in 250 ml NaCl 3% ging -in vergelijking met de toediening in 85 ml NaCl 3%- gepaard met een geringe afname van de plasmaklaring van vrij platina, een toename van de fractie vrij platina aan het eind van het cisplatine-infuus en een toename van de cumulatieve uitscheiding van platina in de urine. De plasma chloride concentratie aan het eind van het cisplatine-infuus was significant hoger na toediening in 250 ml hypertoon zout dan na toediening in 85 ml hypertoon zout. Tevens werd een duidelijke correlatie gevonden tussen plasma chloride concentratie en de vrije platinafractie aan het eind van het infuus (R^2 = 0,43; P = 0,004), alsmede een omgekeerde correlatie tussen plasma chloride concentratie en plasmaklaring van vrij platina (R^2 = 0,39; P = 0,008). Het vehikel waarin cisplatine wordt toegediend bleek derhalve van invloed op de farmacokinetiek van dit geneesmiddel. De bevindingen konden worden verklaard door een tragere omzetting van het (gechloreerde) cisplatine in de sterker aan eiwit bindende gehydrateerde platinaverbindingen onder invloed van het extra aanbod van chloride in het vehikel.

CONCLUSIES

Dosisintensieve behandeling met wekelijks cisplatine in een dosis van 70-80 mg/m^2 toegediend in een hypertone zoutoplossing is haalbaar en effectief gebleken. Bovendien is cisplatine 70 mg/m^2 wekelijks goed te combineren met paclitaxel wekelijks of eenmaal per 4 weken. Dit schema heeft een opmerkelijke antitumor activiteit bij patiënten met eierstokkanker, ook als er sprake is van een recidief na of progressie tijdens standaard platinum bevattende chemotherapie. Een dosisintensieve behandeling met cisplatine kan derhalve worden overwogen bij patiënten met een platinumrefractair ovariumcarcinoom. Afhankelijk van de chemotherapeutische voorbehandeling kan de behandeling worden

gecombineerd met paclitaxel of etoposide. De plaats van dosisintensieve cisplatinetherapie in de behandeling van andere tumoren is nog niet vastgesteld.

Risicofactoren voor toxiciteit van behandeling met wekelijks cisplatine verschillen per bijwerking. Nierfunctieverlies is geassocieerd met hogere leeftijd, vrouwelijk geslacht, roken, verlaagd serum albuminegehalte en gelijktijdige behandeling met paclitaxel. Predisponerende factoren ten aanzien van neuropathie zijn gelijktijdige behandeling met paclitaxel en behandeling met carbo- of cisplatine in de voorgeschiedenis. Symptomatisch gehoorverlies treedt vaker op indien er bij aanvang van de behandeling sprake is van bloedarmoede. Echter, géén van de bovengenoemde risicofactoren moet worden beschouwd als absolute contraindicatie voor wekelijkse, dosisintensieve behandeling met cisplatine.

Traditioneel wordt de dosis cisplatine geïndividualiseerd naar lichaamsoppervlak. Echter, gebleken is dat de correlatie tussen cisplatineklaring en lichaamsoppervlak dermate zwak is dat deze gewoonte niet kritiekloos kan worden voortgezet. Andere patiëntgebonden factoren als leeftijd, geslacht, hematocriet, plasmaconcentraties totaal eiwit en albumine, en creatinineklaring hadden in een populatiekinetiekmodel geen invloed op verdelingsvolume en plasmaklaring van cisplatine. In een relatief kleine studie werd aangetoond dat het volume hypertoon zout waarin cisplatine wordt toegediend van invloed is op de farmacokinetiek, waarbij een groter volume hypertoon zout gepaard ging met een toegenomen fractie vrij platina in het plasma en een toegenomen cumulatieve uitscheiding van platina in de urine. Bovendien werd een verband gevonden tussen plasma chloride concentraties en de farmacokinetiek van cisplatine. In hoeverre de plasma chloride concentratie in tegenstelling tot alle andere bovengenoemde factoren wel een voorspellende waarde heeft met betrekking tot farmacokinetiek, toxiciteit en/of antitumor activiteit van behandeling met cisplatine is een goed aanknopingspunt voor nader onderzoek. Op grond van de huidige gegevens is dosisindividualisatie bij volwassen patiënten die met cisplatine behandeld worden niet rationeel. Uitgaande van een cisplatinedosis van 50-100 mg/m^2 en een lichaamsoppervlak van 1,86 ± 0,19 m^2 in de onderzochte patiëntenpopulatie kan voor de meeste volwassen patiënten een gefixeerde dosis worden gebruikt volgens onderstaande tabel:

Dosis cisplatine (in mg per m^2)	Dosis cisplatine (in mg)
50	95
60	110
70	130
75	140
80	150
100	185

In hoeverre een gefixeerde dosis onafhankelijk van lichaamsoppervlak veilig toepasbaar is bij patiënten met een extreem klein (< 1,6 m^2) of extreem groot (> 2,1 m^2) lichaamsoppervlak wordt thans onderzocht in een prospectieve farmacokinetische studie.

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CURRICULUM VITAE

Felix Ernst de Jongh werd op 1 oktober 1966 geboren te Leiden. In 1984 behaalde hij het diploma Voorbereidend Wetenschappelijk Onderwijs aan de Christelijke Scholengemeenschap "Comenius" te Capelle aan den IJssel. Hierna begon hij met de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam. Tijdens zijn studie was hij student-assistent bij het project "ERCP en afwijkingen van pancreas, galwegen en duodenum" in het Academisch Ziekenhuis Dijkzigt. Na het doctoraalexamen (cum laude) in 1988 volgde hij een onderzoekstage bij de Dienst Neurologie en Neurofysiologie van het Universitair Ziekenhuis te Gent, België (Prof. Dr. J. de Reuck en Dr. L. Crevits). Na afronding van de co-assistentschappen verrichtte hij onder supervisie van Prof. Dr. S.W. Schalm in het Academisch Ziekenhuis Dijkzigt onderzoek naar het beloop van chronische hepatitis B. In januari 1991 behaalde hij het artsexamen (cum laude), waarna de dienstplicht werd vervuld als officier-arts bij de Koninklijke Marine. In april 1992 begon hij als AGNIO Interne Geneeskunde, Cardiologie en Longziekten in het Havenziekenhuis te Rotterdam. In januari 1994 startte hij in hetzelfde ziekenhuis met de opleiding tot internist (opleider: Dr. A.G.C. Bauer). Vanaf januari 1996 werd de opleiding voortgezet in het Sint Franciscus Gasthuis te Rotterdam (opleider: Dr. H.S.L.M. Tjen). Het laatste deel van de opleiding tot internist werd vanaf januari 1998 gevolgd in het Academisch Ziekenhuis te Rotterdam (opleider: Prof. J.H.P. Wilson). In mei 1999 begon hij in de Daniel den Hoed Kliniek met de opleiding Medische Oncologie (opleider: Prof. Dr. G. Stoter); in november 1999 werd aangevangen met het onderzoek dat heeft geleid tot dit proefschrift (promotor: Prof. Dr. J. Verweij). Registratie als internist vond plaats op 1 januari 2000 en als medisch oncoloog op 10 oktober 2001. Vanaf oktober 2001 is hij werkzaam als internist met aandachtsgebied oncologie in het Ikazia Ziekenhuis te Rotterdam. Hij is gehuwd met Simone Hartong; samen zijn zij de gelukkige ouders van twee prachtige dochters, Mieke en Iris.

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