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

FE de Jongh1,4, RN van Veen1, SJ Veltman1, R de Wit1, MEL van der Burg1, MJ van den Bent2, ASTh Planting1, WJ Graveland1, G Stoter1 and J Verweij*1
1Department of Medical Oncology, Daniel den Hoed Cancer Center, Erasmus University Medical Center Rotterdam, PO Box 5201, 3008 AE Rotterdam, The Netherlands; 2Department of Neuro-Oncology, Daniel den Hoed Cancer Center, Erasmus University Medical Center Rotterdam, 3008 AE Rotterdam, The Netherlands; 3Department of Biostatistics, Daniel den Hoed Cancer Center, Erasmus University Medical Center Rotterdam, 3008 AE Rotterdam, The Netherlands

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. Leukopenia 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.

British Journal of Cancer (2003) 88, 1199 – 1206. doi:10.1038/sj.bjc.6600884 www.bjcancer.com

© 2003 Cancer Research UK

Keywords: cisplatin; chemotherapy; toxicity; prognostic factors

CIS-Diaminedichloro platinum (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 5HT3-receptor antagonists and vigorous hydration (Pinzani et al., 1994). Administration of cisplatin in hypertonic saline may further alleviate nephrotoxic side effects (Ozols et al., 1984). 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 (Cersosimo, 1989) and ototoxicity (Laurell and Jungnelius, 1990) 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 (Planting et al., 1993, 1994, 1995a, b, 1997a, b; van der Burg et al., 1998; van den Bent et al., 1999, 2002).

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 (Planting et al., 1993, 1994, 1995a, b, 1997a, b; van der Burg et al., 1998; van den Bent et al., 1999). All study protocols were approved by the Institutional Ethics Board and all participating patients gave written informed consent.
Clinical 1200/C0 and administered by i.v. infusion over 3 h. Patients received i.v. paclitaxel. Cisplatin powder was dissolved in 250 ml NaCl 3% platelets prophylaxis consisted of a 5HT 3 antagonist in combination with creatinine clearance was estimated using the Cockroft and Gault clearance measured by 24-h urine collection. In addition, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), included haemoglobin, WBC, granulocytes, platelets, albumin, and cytotoxic comedication (etoposide, paclitaxel or none). 

**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 11 normal saline or dextrose-saline and posthydration with 31 normal saline or dextrose-saline supplemented with KCl (20 mmol l⁻¹) and MgSO₄ (2 g l⁻¹). Antiemetic prophylaxis consisted of a 5HT₃ 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 × 10⁹ l⁻¹ and/or platelets <75 × 10⁹ l⁻¹. When used in combination with etoposide, cisplatin administration was postponed in the case of WBC <2.5 × 10⁹ l⁻¹ and/or platelets <75 × 10⁹ l⁻¹ on day 8 or day 36, WBC <1.5 × 10⁹ l⁻¹ and/or platelets <50 × 10⁹ l⁻¹ on day 15 or day 43, and WBC <3.0 × 10⁹ l⁻¹ and/or platelets <100 × 10⁹ l⁻¹ on day 29. With the cisplatin/paclitaxel regimen, treatment was postponed if WBC <1.0 × 10⁹ l⁻¹ and/or platelets <50 × 10⁹ l⁻¹ on days 8, 15, 36 or 43, and if on day 29 WBC <3.0 × 10⁹ l⁻¹ and/or platelets <100 × 10⁹ l⁻¹. Cisplatin was discontinued if creatinine clearance fell below 45 ml min⁻¹ 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 (Planting et al, 1993, 1994, 1995a, b, 1997a, b; van der Burg et al, 1998, 2002; van den Bent et al, 1999). 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 two 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%), seven with 3 weeks delay (2%) and two with 4 weeks delay (0.5%). From the patients that received four (n = 30) or five (n = 39) administrations of cisplatin, 55 had no treatment delay (14%), 18 had 1 week delay (4.5%), 10 had 2 weeks delay (2.5%) and six 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 two had a 1-week treatment delay (0.5%). The mean number of cisplatin administrations was 5.3, with a median total cisplatin dose of 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⁻¹ (range, 10–80 mg m⁻² week⁻¹; mean, 55.7 ± 11.6 mg m⁻² week⁻¹).

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...
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 (8)             |
| Unknown           | 3 (1)              |
| **Tumour type**   |                     |
| Head and neck cancer | 155 (39)   |
| Ovarian cancer    | 108 (27)           |
| CUP               | 47 (12)            |
| NSCLC             | 36 (9)             |
| Mesothelia        | 24 (6)             |
| Glioma            | 18 (4)             |
| Miscellaneous     | 12 (3)             |
| **Prior chemotherapy** |                |
| None              | 308 (77)           |
| Platinum-based    | 88 (22)            |
| Nonplatinum-based | 4 (1)              |

WHO=World Health Organization; CUP=Carcinoma with unknown primary; NSCLC=nonsmall 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 |
| Nephrotoxicity | 27 | 34 | 17 | 14 | 8  |
| Nausea     | 18 | 44 | 30 | 8  | 0  |
| Vomiting   | 36 | 30 | 27 | 6  | 1  |
| Hypomagnesaemia | 59 | 32 | 8  | 1  | 0  |
| Hypokalaemia | 55 | 23 | 18 | 3  | 1  |
| Hypocalcaemia | 58 | 15 | 1  | 0  | 0  |
| Neurotoxicity | 53 | 36 | 8  | 3  | 0  |
| Ototoxicity| 58 | 27 | 14 | 1  |    |

*Common Toxicity Criteria, Version 1.0, National Cancer Institute. *Auditory was not routinely performed; grade 0 ototoxicity should be interpreted as grade D or E.

Nephrotoxicity

At baseline, serum creatinine (mean±standard deviation) was 84±14 μmol l⁻¹ with an estimated creatinine clearance of 83±22 ml min⁻¹. After three and six administrations of weekly cisplatin, the serum creatinine was 93±40 and 102±29 μmol l⁻¹ respectively with an estimated creatinine clearance of 77±23 and 69±23 ml min⁻¹ 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⁻¹ (range, 0.51–1.33 mmol l⁻¹), 2.39±0.14 mmol l⁻¹ (range, 1.92–3.03 mmol l⁻¹), 139±3.7 mmol l⁻¹ (range, 128–149 mmol l⁻¹) and 4.2±0.41 mmol l⁻¹ (range, 2.8–5.5 mmol l⁻¹) at baseline to 0.70±0.13 mmol l⁻¹ (range, 0.22–1.62 mmol l⁻¹), 2.26±0.15 mmol l⁻¹ (range, 1.59–2.69 mmol l⁻¹), 135±4.3 mmol l⁻¹ (range, 117–146 mmol l⁻¹) and 4.0±0.50 mmol l⁻¹ (range, 2.5–5.2 mmol l⁻¹) after three administrations, and 0.62±0.14 mmol l⁻¹ (range, 0.23–1.16 mmol l⁻¹), 2.24±0.16 mmol l⁻¹ (range, 1.53–2.69 mmol l⁻¹), 135±4.3 mmol l⁻¹ (range, 122–146 mmol l⁻¹) and 4.0±0.56 mmol l⁻¹ (range, 2.2–5.6 mmol l⁻¹) 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 a ≥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 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 (OR¼4.0, P¼0.001), hypoalbuminaemia (OR¼3.5, P¼0.006) and smoking (OR¼2.5, P¼0.002) 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⁻¹ (P¼0.007). 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 (OR¼2.0, P¼0.02).

Haematological toxicity

In 37 patients (9%), weekly cisplatin treatment was discontinued because of haematological toxicity, in the majority of them (21 patients, 7%), ototoxicity (10 patients, 2.5%), neurotoxicity (four patients, 1%), gastrointestinal toxicity (three patients, 1%), cardiovascular complications (two 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; nine of them had rapidly progressive disease.

Neurotoxicity

Clinical data on neurotoxicity (according to CTC criteria) were fully available for the period of weekly cisplatin treatment, but

Toxicity analysis of weekly cisplatin chemotherapy

FE de Jongh et al

British Journal of Cancer (2003) 88(8), 1199 – 1206
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 (8%) grade 2, nine patients (2%) grade 3, and one 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, non-smoking and alcohol consumption ≤2 units day⁻¹ (Table 4). After adjustment for prior chemotherapy and cytotoxic co-treatment, 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).

### 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⁻¹, it can be concluded that a short intensive weekly cisplatin schedule is a

---

**Table 3** Logistic regression analysis for nephrotoxicity

| Baseline parameter | Odds ratio (CI) | P-value | Odds ratio (CI) | P-value |
|--------------------|----------------|---------|----------------|---------|
| 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 co-treatment | 3.46 (1.80–6.66) | <0.001 | |
| Etoposide co-treatment | 1.11 (0.66–1.88) | 0.687 | |
| Weight loss >5% | 0.99 (0.61–1.62) | 0.978 | |
| Smoking | 1.21 (0.75–1.97) | 0.436 | |
| Alcohol intake >2 units day⁻¹ | 1.25 (0.76–2.03) | 0.370 | |
| Systolic blood pressure >150 mmHg | 1.44 (0.82–2.52) | 0.206 | |
| Diastolic blood pressure >90 mmHg | 0.68 (0.34–1.38) | 0.287 | |
| Creatinine clearance <70 ml min⁻¹ | 1.24 (0.77–2.01) | 0.378 | |
| Hyponatraemia (<135 mmol l⁻¹) | 0.99 (0.50–1.96) | 0.968 | |
| Hypokalaemia (<2.2 mmol l⁻¹) | 1.36 (0.79–2.33) | 0.271 | |
| Hypocalcaemia (<0.7 mmol l⁻¹) | 0.95 (0.39–2.29) | 0.907 | |
| Hypomagnesaemia (<0.7 mmol l⁻¹) | 2.15 (0.80–5.79) | 0.129 | |
| Anaemia (haemoglobin <135 g l⁻¹) | 0.95 (0.61–1.49) | 0.826 | |
| Hypoaetobinaemia (<135 g l⁻¹) | 3.13 (1.36–7.22) | 0.007 | |
| Alkaline phosphatase | 1.85 (0.93–3.65) | 0.078 | |
| AST > normal | 1.61 (0.65–3.99) | 0.308 | |
| ALT > normal | 1.83 (0.91–3.67) | 0.091 | |
| LDH > normal | 1.10 (0.64–1.89) | 0.734 | |

Multivariate analysis

| Independent risk factor | Odds ratio (CI) | P-value |
|-------------------------|----------------|---------|
| Paclitaxel co-treatment | 4.01 (1.83–8.77) | 0.001 |
| Smoking | 2.50 (1.39–4.51) | 0.002 |
| Hypoaetobinaemia | 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 |

---

*Nephrotoxicity defined as ≥25% decline in estimated creatinine clearance (Cockroft-Gault). bAdjusted for prior chemotherapy and cytotoxic co-treatment (paclitaxel, etoposide). CI = 95% confidence interval; BSA = body-surface area; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase.
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 cotreatment) 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 neurotoxicity than the alternate sequence, which was first ascribed to lower paclitaxel clearance rates after cisplatin administration (Litterst, 1981). The infusion of cremophor EL immediately before cisplatin administration ameliorated leucopenia, neutropenia and thrombocytopenia (Gelderblom et al, 2002), 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 the upper limit of the 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⁻¹ at baseline to 69 ± 23 ml min⁻¹ 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 (Planting et al, 1993, 1997a, b). 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 (Litterst, 1981). The most likely explanation is that

### Table 4 Logistic regression analysis for neurotoxicity

| Baseline parameter | Unadjusted | Adjusted | P-value | P-value |
|--------------------|------------|----------|---------|---------|
| **Univariate analysis** |            |          |         |         |
| Age (year⁻¹)       | 1.03 (0.99 – 1.07) | 1.02 (0.98 – 1.06) | 0.129 | 0.866 |
| Sex (female)       | 4.73 (2.01 – 11.2) | 1.53 (0.50 – 4.65) | <0.001 | 0.452 |
| BSA (m²)           | 0.48 (0.07 – 3.12) | 0.68 (0.06 – 7.41) | 0.442 | 0.750 |
| Performance status > 1 | 1.42 (0.40 – 5.11) | 1.23 (0.29 – 5.22) | 0.589 | 0.780 |
| Tumour type (ovarian cancer) | 8.69 (3.19 – 23.6) | 4.57 (0.63 – 35.2) | <0.001 | 0.133 |
| Prior carboplatin treatment | 4.07 (1.71 – 9.68) | 1.13 (0.43 – 2.98) | 0.001 | 0.809 |
| Prior cisplatin treatment | 6.48 (2.63 – 16.0) | 2.00 (0.79 – 5.06) | <0.001 | 0.144 |
| Paclitaxel coadministration | 8.33 (2.43 – 28.5) | 2.04 (0.58 – 7.34) | 0.045 | 0.268 |
| Paclitaxel cotreatment | 15.3 (4.89 – 47.9) | 0.68 (0.06 – 7.41) | <0.001 | 0.203 |
| Etoposide cotreatment | 2.12 (0.67 – 6.76) | 0.46 (0.16 – 1.34) | 0.03 | 0.153 |
| Weight loss > 5%    | 0.85 (0.39 – 1.80) | 0.42 (0.12 – 1.43) | 0.003 | 0.167 |
| Smoking             | 0.23 (0.09 – 0.60) | 0.017 | 0.003 | 0.144 |
| Alcohol intake > 2 units per day | 0.27 (0.09 – 0.79) | 0.176 | 0.46 (0.16 – 1.34) | 0.133 |
| Systolic blood pressure > 150 mmHg | 1.72 (0.78 – 3.79) | 1.32 (0.52 – 3.34) | 0.001 | 0.556 |
| Diastolic blood pressure > 90 mmHg | 0.35 (0.08 – 1.51) | 0.35 (0.07 – 1.66) | 0.140 | 0.872 |
| Creatinine clearance < 70 μmol l⁻¹ | 1.72 (0.84 – 3.53) | 1.07 (0.47 – 2.45) | 0.214 | 0.678 |
| Hypomagnesaemia (<0.7 mmol l⁻¹) | 0.94 (0.49 – 1.81) | 0.72 (0.15 – 3.39) | 0.361 | 0.303 |
| Hypocalcaemia (<2.2 mmol l⁻¹) | 1.85 (0.59 – 5.82) | 0.56 (0.19 – 1.69) | 0.001 | 0.268 |
| Hypophosphatasa (<135 mg l⁻¹) | 0.48 (0.06 – 3.77) | 2.06 (0.58 – 7.34) | <0.001 | 0.268 |
| Anaemia (haemoglobin < normal) | 1.09 (0.54 – 2.20) | 1.84 (0.80 – 4.20) | <0.001 | 0.149 |
| Hypoalbuminaemia (<35 g l⁻¹) | 0.82 (0.18 – 3.69) | 0.81 (0.15 – 3.96) | 0.864 | 0.754 |
| AST > normal        | 0.43 (0.10 – 1.89) | 0.27 (0.03 – 2.53) | 0.266 | 0.252 |
| ALT > normal        | 1.37 (0.50 – 3.79) | 1.27 (0.29 – 5.53) | 0.518 | 0.753 |
| LDH > normal        | 1.07 (0.46 – 2.47) | 1.08 (0.34 – 3.47) | 0.871 | 0.892 |

### Multivariate analysis

| Independent risk factor | Odds ratio (CI) | P-value | Odds ratio (CI) | P-value |
|-------------------------|----------------|---------|----------------|---------|
| Paclitaxel cotreatment  | 8.33 (2.43 – 28.5) | 0.001 | 3.50 (1.29 – 9.48) | 0.014 |
| Prior cisplatin treatment | 3.88 (1.38 – 10.9) | 0.10 | 3.50 (1.29 – 9.48) | 0.014 |

*Neurotoxicity defined as CTC grade 2–4. **Adjusted for prior chemotherapy and cytotoxic cotreatment (paclitaxel, etoposide). CI=95% confidence interval; BSA=body-surface area; AST=aspartate aminotransferase; ALT=alanine aminotransferase; LDH=lactate dehydrogenase.*
Influence on this clearance. Paclitaxel coadministration was 15% higher in men than in women but age had no significant biological mechanism remains a matter of speculation. It is known, 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 (Maytin et al, 1999), 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 (Stewart et al, 1997). Another strong predisposing factor for renal toxicity was hypoalbuminaemia. This has also been described for patients receiving conventional cisplatin treatment (Stewart et al, 1997). 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 (Reece et al, 1987; Nagai et al, 1996; Nagai and Ogata, 1997). 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
de Jongh FE, Verweij J, Loos WJ, de Wit R, de Jonge MJA, Planting AST, Nooter K, Stoter G, Sparreboom A (2001) Body-surface area-based dosing does not increase accuracy of predicting cisplatin exposure. J Clin Oncol 19: 3733–3739
de Vos AI, Nooter K, Verweij J, Loos WJ, Brouwer E, de Bruijn P, Ruigrok EJ, van der Burg MEL, Stoter G, Sparreboom A (1997) Differential modulation of cisplatin accumulation in leukocytes and tumor cell lines by the paclitaxel vehicle Cremophor EL. Ann Oncol 8: 1145–1150
Earhart RH, Martin PA, Tutsch KD, Erturk E, Wheeler RH, Bull FE (1983) Improvement in the therapeutic index of cisplatin (NSC 119875) by pharmacologically induced chloruresis in the rat. Cancer Res 43: 1187–1194
Gelderblom H, Loos WJ, Verweij J, van der Burg MEL, de Jonge MJA, Brouwer E, Nooter K, Stoter G, Sparreboom A (2002) Modulation of cisplatin pharmacodynamics by Cremophor EL: experimental and clinical studies. Eur J Cancer 38: 205–213
Hilkens PHE, Planting AST, van der Burg MEL, Moll JWB, van Putten WLJ, Vecht CJ, van den Bent MJ (1994) Clinical course and risk factors of cisplatin-induced ototoxicity. Ann Oncol 5: 1194–1198

REFERENCES

Bajorin DF, Bosj GJ, Alcock NW, Niedzwiecki D, Gallina E, Shurgot B (1986) Pharmacokinetics of cis-diaminedichloroplatinum(II) after administration in hypertensive saline. Cancer Res 46: 5969–5972
Blakley BW, Gupta AK, Myers SI, Schwan S (1994) Risk factors for cisplatin-induced ototoxicity. Arch Otolaryngol Head Neck Surg 120: 541–546
Cavaletti G, Marzorati L, Bogliu G, Colombo N, Marzola M, Pitelli MR, Tredici G (1992) Cisplatin-induced peripheral neurotoxicity is dependent on total-dose intensity and single-dose intensity. Cancer 69: 203–207
Cersosimo RJ (1989) Cisplatin neurotoxicity. Cancer Treat Rev 16: 195–211
Connolly E, Markman M, Kennedy A, Webster K, Kulp B, Peterson G, Belinson J (1996) Paclitaxel delivered at a 3-hr infusion with cisplatin in patients with gynecologic cancers: unexpected incidence of neurotoxicity. Gynecol Oncol 62: 166–168
de Jongh FE, Verweij J, Loos WJ, de Wit R, de Jonge MJA, Planting AST, Noooter K, Stoter G, Sparreboom A (2001) Body-surface area-based
neurotoxicity following cisplatin in an intensive dosing schedule. *Eur J Neurol* 1: 45 – 50

Hilkens PHE, Pronk LC, Verweij J, Vecht CJ, van Putten WLJ, van den Bent MJ (1997) Peripheral neuropathy induced by combination chemotherapy of docetaxel and cisplatin. *Br J Cancer* 75: 417 – 422

Hilkens PHE, van der Burg MEL, Moll JW, Planting AST, van Putten WLJ, Vecht CJ, van den Bent MJ (1995) Neurotoxicity is not enhanced by increased dose intensities of cisplatin administration. *Eur J Cancer* 31A: 678 – 681

Jones MM, Basinger MA, Beatty JA, Holscher MA (1997a) A phase II study of weekly high-dose cisplatin combined with long term oral etoposide in advanced solid tumours. *Br J Cancer* 68: 789 – 792

Lagrange JL, Médecin B, Etienne MC, Pivot X, Cassuto-Viguier E, Renée N, Thys A, Ferrero JM, Otto J, François E, Milano G (1997) Cisplatin nephrotoxicity: a multivariate analysis of potential predisposing factors. *Pharmacother* 17: 1246 – 1253

Laurell G, Jungnelius U (1990) High-dose cisplatin treatment: hearing loss and plasma concentrations. *Laryngoscope* 100: 724 – 734

Litterer CL (1981) Alterations in the toxicity of cis-dichlorodiammineplatinum II and in tissue localization of platinum as a function of NaCl concentration in the vehicle of administration. *Toxicol Appl Pharmacol* 61: 99 – 108

Martín M, Leopold J, Losočalzo J (1999) Oxidant stress in the vasculature. *Curr Atheroscler Rep* 1: 156 – 164

Merozani A, Davidson SA, Schrier RW (1997) Increased nephrotoxicity of combination taxol and cisplatin chemotherapy in gynecologic cancers as compared to cisplatin alone. *Am J Nephrol* 17: 53 – 58

Nagai N, Yoshida M, Ogata H, Tsuchino D, Wada Y, Someya K, Ohno T, Masuhara K, Tanaka Y, Kato K, Nagai H, Yokoyama A, Kurita Y (1996) Relationship between pharmacokinetics of unchanged cisplatin and nephrotoxicity after intravenous infusions of cisplatin to cancer patients. *Cancer Chemother Pharmacol* 39: 131 – 137

Nagai N, Ogata H (1997) Quantitative relationship between pharmacokinetics of unchanged cisplatin and nephrotoxicity in rats: importance of area under the concentration – time curve (AUC) as the major toxicodynamic determinant in vivo. *Cancer Chemother Pharmacol* 40: 11 – 18

Ozols RF, Corden BJ, Jacob J, Wesley MN, Ostchega Y, Young RC (1984) High-dose cisplatin in hypertonic saline. *Ann Intern Med* 100: 19 – 24

Pinzani V, Bressolle F, Haug IJ, Galtier M, Blayac JP, Balmès P (1994) Cisplatin-induced renal toxicity and toxicity-modulating strategies: a review. *Cancer Chemother Pharmacol* 33: 1 – 9

Planting AST, Kho GS, van der Burg MEL, Goey SH, Schellens JHM, van den Bent MJ, van der Gaast A, de Boer-Dennert M, Stoter G, Verweij J (1997a) A phase II study of weekly high-dose cisplatin combined with oral etoposide in advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* 40: 347 – 352

Planting AST, de Mulder PHM, de Graeff A, Verweij J (1997b) Phase II study of weekly high-dose cisplatin for six cycles in patients with locally advanced squamous cell carcinoma of the head and neck. *Eur J Cancer* 33: 61 – 65

Planting AST, Schellens JHM, Goey SH, van der Burg MEL, de Boer-Dennert M, Stoter G, Verweij J (1994) Weekly high-dose cisplatin in malignant pleural mesothelioma. *Ann Oncol* 5: 373 – 374

Planting AST, van der Burg MEL, de Boer-Dennert M, Stoter G, Verweij J (1993) Phase I/II study of a short course of weekly cisplatin in patients with advanced solid tumours. *Br J Cancer* 68: 190 – 192

Planting AST, van der Burg MEL, Goey SH, Schellens JHM, van den Bent MJ, de Boer-Dennert M, Stoter G, Verweij J (1995a) Phase I study of weekly high-dose cisplatin combined with long term oral etoposide in advanced solid tumors. *Ann Oncol* 6: 613 – 615

Reddel RR, Kefferd RF, Grant JM, Coates AS, Fox RM, Tattersall HN (1982) Ototoxicity in patients receiving cisplatin: importance of dose and method of drug administration. *Cancer Treat Rep* 66: 19 – 23

Reece PA, Stafford I, Russell J, Khan M, Gill PG (1987) Creatinine clearance as a predictor of ultrafilterable platinum disposition in cancer patients treated with cisplatin: relationship between peak ultrafilterable platinum plasma levels and nephrotoxicity. *J Clin Oncol* 5: 304 – 309

Rowinsky EK, Gilbert MR, McGuire WP, Noe DA, Grochow LB, Forastiere AA, Ettinger DS, Lubejko BG, Clark B, Sartorius SE, Cornblath DR, Hendricks CR, Donehower RC (1991) Sequences of taxol and cisplatin: a phase I and pharmacologic study. *J Clin Oncol* 9: 1692 – 1703

Schaeffer SD, Post JD, Close LG, Wright GG (1985) Ototoxicity of low- and moderate-dose cisplatin. *Cancer* 56: 1934 – 1939

Stewart DJ, Duberg CB, Mikhail NZ, Redmond D, Montpetit VAJ, Goel R (1997) Association of cisplatin nephrotoxicity with patient characteristics and cisplatin administration methods. *Cancer Chemother Pharmacol* 40: 293 – 308

van den Bent MJ, Pronk L, Sillevis Smitt PA, Vecht CJ, Eskens FA, Verweij J (1999) Phase II study of weekly dose-intensified cisplatin chemotherapy with oral etoposide in recurrent glioma. *J Neuro-oncol* 44: 59 – 64

van den Bent MJ, van Putten WLJ, Hilkens PHE, de Wit R, van der Burg MEL (2002) Retreatment with dose-dense weekly cisplatin after previous cisplatin chemotherapy is not complicated by significant neuro-toxicity. *Eur J Cancer* 38: 387 – 391

van der Burg MEL, de Wit R, Stoter G, Verweij J (1998) Phase I study of weekly cisplatin and weekly or 4-weekly taxol: a highly active regimen in advanced epithelial ovarian cancer. *Proc Am Soc Clin Oncol* 17: abstract 1370

van der Burg MEL, de Wit R, van Putten WLJ, Logmans A, Kruit WHJ, Stoter G, Verweij J (2002) Weekly cisplatin and daily oral etoposide is highly effective in platinum pretreated ovarian cancer. *Br J Cancer* 86: 19 – 25