

# Continuous ambulatory peritoneal dialysis: pharmacokinetics and clinical outcome of paclitaxel and carboplatin treatment

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Received: 12 November 2007 / Accepted: 21 December 2007 / Published online: 19 January 2008  
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## Abstract

**Purpose** Administration of chemotherapy in patients with renal failure, treated with hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) is still a challenge and literature data is scarce. Here we present a case study of a patient on CAPD, treated with weekly and three-weekly paclitaxel/carboplatin for recurrent ovarian cancer.

**Experimental** During the first, second and ninth cycle of treatment, blood, urine and CAPD samples were collected for pharmacokinetic analysis of paclitaxel and total and unbound carboplatin-derived platinum.

**Results** Treatment was well tolerated by the patient. No excessive toxicity was observed and at the end of treatment she was in a complete remission. The plasma pharmacokinetics of paclitaxel were unaltered compared to historical data, with neglectable urinary and CAPD clearance. In contrast, the pharmacokinetics of carboplatin were altered, with doubled half-lives compared to patients with normal renal function. Of the administered carboplatin dose, up to 20% was cleared via the dialysate, while only up to 8% was cleared via the urine.

**Conclusion** Paclitaxel and carboplatin can be safely administered to patients with chronic renal failure on

CAPD. For paclitaxel the generally applied dose can be administered, and although for carboplatin dose-adjustment is required due to the diminished renal function, the dose can be calculated using Calvert's formula.

**Keywords** CAPD · Paclitaxel · Carboplatin · Pharmacokinetic · Ovarian cancer

## Introduction

Platinum-based chemotherapy is commonly accepted as the standard first line treatment for ovarian cancer. Because of a more favorable toxicity profile, carboplatin is frequently preferred over cisplatin [7, 16, 24, 25, 27, 29]. Carboplatin is mainly cleared (70%) by renal excretion, with most of the drug excreted unchanged in the urine over the first 24 h in patients with a normal renal function (i.e., GFR 33–135 mL/min) [15]. The renal clearance of carboplatin, in patients with a normal renal function, is dependent on the glomerular filtration rate (GFR). Calvert [3] showed in pharmacokinetic studies that the renal clearance of carboplatin is linearly related to the GFR and ever since than carboplatin doses are commonly calculated by Calvert's formula [3] (Eq. 1). In the formula, the drug's exposure, expressed as the area under concentration time curve (AUC), is a set value, depending on the chemotherapy schedule used.

$$\text{Dose (mg)} = \text{Target AUC (mg/mL} \times \text{min)} \\ \times [\text{GFR (mL/min)} + 25] \quad (1)$$

Calvert's formula has been developed using data of cancer patients with GFR from 33 to 135 mL/min, in which the GFR is measured using the <sup>51</sup>Cr-EDTA clearance. However, due to the expensive and patient-inconvenient use of the <sup>51</sup>Cr-EDTA clearance, the GFR is

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commonly estimated using, among others, the Cockcroft–Gault formula [5]. The substitution of the method for the estimation of the GFR is questionable and results in less predictive estimations of the carboplatin clearance [9] and it is still unknown whether Calvert's formula may also be used for patients with GFR less than 10 mL/min and on continuous ambulatory peritoneal dialysis (CAPD).

In ovarian cancer carboplatin is mostly combined with paclitaxel in view of the proven added value of the latter [29]. Paclitaxel is extensively metabolized by hepatic cytochrome P450 enzymes and is mainly cleared by biliary secretion, with less than 10% excreted by the kidneys [21].

Studies describing the pharmacokinetics of carboplatin and/or paclitaxel in patients with renal failure are scarce [1, 4, 6, 10, 17, 19, 21, 31, 32, 35–37]. As paclitaxel is predominantly cleared by hepatic metabolism and biliary excretion, it was concluded that there is no need for dose adjustment of paclitaxel in patients with renal failure [1, 19, 32, 37]. Furthermore, it was shown that Calvert's formula could be safely applied in patients with minimal renal function (i.e., GFR values less than 10 mL/min) and on hemodialysis, in which carboplatin is cleared via the dialysate [4, 12, 35]. In patients on hemodialysis the GFR is set at zero in Calvert's formula (Eq. 1) to calculate the dose, while the hemodialysis is started within 24 h after the start of infusion [21].

Publications, supporting safe and efficient therapies of (cytotoxic) anticancer agents in patients on CAPD are even more scarce [12, 20, 34]. To the best of our knowledge, to date no reports have been published describing the pharmacokinetics of paclitaxel in patients on CAPD, while the pharmacokinetics of carboplatin have been described in a single pediatric patient on CAPD [12], in which it was concluded that carboplatin was not cleared by peritoneal dialysis.

Here, we report on the pharmacokinetics of carboplatin and paclitaxel in plasma, urine and peritoneal dialysate as well as the clinical data of a patient with recurrent ovarian cancer on CAPD.

## Patient and methods

### Patient

A 49-year-old Caucasian female was diagnosed with ovarian cancer FIGO stage IIIc in 2002. The initial treatment consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy and resection of all macroscopic tumor lesions. Postoperatively treatment consisted of nine cycles of three-weekly paclitaxel and carboplatin. The patient had preexistent

moderate renal failure (creatinine 200  $\mu\text{mol/L}$ ), most probably due to longstanding hypertension. At the end of the treatment a clinical complete remission of the ovarian cancer was observed. During follow-up her renal function deteriorated progressively and in 2004 she developed end-stage renal failure for which chronic ambulatory peritoneal dialysis was started. In 2005 she presented with increasing plasma concentrations of the tumor marker CA 125 and a few months later she had clinical progressive disease with liver, spleen and lung metastases and also retroperitoneal and inguinal lymph nodes metastases.

By that time she dialyzed four times a day, using 2 L bags of dialysis fluid, in a scheme of twice daily 1.36% glucose, once 2.27% glucose, each remaining 4–6 h in the peritoneal cavity. During the night she used 7.5% glucose (extraneal), which remained the peritoneal cavity for at least 6 h.

She was then treated with six-weekly cycles of dose-dense induction chemotherapy consisting of paclitaxel 90  $\text{mg/m}^2$ , administered over 1 h, followed by a 1 h infusion of carboplatin targeted at AUC 4 [2, 33]. At start of therapy, while the patient was continuously treated with peritoneal dialysis, serum creatinine was 778  $\mu\text{mol/L}$ .

Subsequently, according to the protocol, in which after induction chemotherapy with dose-dense weekly paclitaxel carboplatin treatment is changed into standard three-weekly paclitaxel carboplatin, she received six cycles of three-weekly paclitaxel 175  $\text{mg/m}^2$ , administered over 3 h, followed by a 1 h infusion of carboplatin at AUC 5. The dose of carboplatin was calculated using Calvert's formula (Eq. 1, [3]) in which the GFR was calculated according to the Cockcroft Gault formula [5]. Pharmacokinetics were performed. Because of renal failure, she was already treated with erythropoietin at a dose of 10,000 IU once a week.

### Pharmacokinetic sampling

For paclitaxel and carboplatin plasma pharmacokinetic analysis, blood samples were collected during the first and second one-weekly cycles and the third three-weekly cycle (i.e. cycle 9) in the presence of lithium heparin as anticoagulant. Samples for paclitaxel analysis were taken at the following time points: before the intravenous infusion, halfway the infusion (i.e., 30 min during the 1 h infusion and 1 h 30 min during the 3 h infusion), at the end of infusion and at 30 min, 1, 2, 4, 6 and 24 h after the end of infusion. Within 15 min after collection, plasma was separated by centrifugation at 3,000g for 10 min, which was stored at  $T < -70^\circ\text{C}$  until analysis. For carboplatin analysis, blood samples were collected at the following time

points: before the intravenous infusion, 30 min after the start of infusion, at the end of the 1 h infusion and at 1, 2, 3, 4 and 21 h after the end of infusion. Within 15 min after collection, plasma was separated by centrifugation at 3,000g for 10 min. Subsequently, 500- $\mu$ L aliquots of the plasma supernatant were mixed with 1.0-mL aliquots of ice-cold ( $-20^{\circ}\text{C}$ ) ethanol and stored at  $T < -20^{\circ}\text{C}$  for a maximum of 24 h. Ethanolic supernatant was collected by centrifugation of the samples at maximum speed in an Eppendorf centrifuge (23,000g) for 5 min after which the clear supernatant was subsequently stored at  $T < -70^{\circ}\text{C}$  until analysis. The remaining plasma supernatant, for the analysis of carboplatin-derived total platinum, was stored at  $T < -70^{\circ}\text{C}$  until analysis.

Peritoneal dialysis samples were also collected in heparinized containers and stored at  $T < -70^{\circ}\text{C}$  until analysis. Samples were collected up to 24 h after the start of the paclitaxel infusion. The time of dialysis as well as the time in the peritoneal cavity and the weight of each dialysis bag was accurately recorded.

Urine samples, 800–1,150 mL per day, were collected during the same time-period in polypropylene containers, from which aliquots were stored at  $T < -70^{\circ}\text{C}$  pending analysis.

#### Carboplatin analysis

Plasma concentrations of unbound carboplatin-derived platinum were determined according to a method as described for cisplatin-derived platinum [22]. For unbound platinum analysis, on the day of analysis aliquots of 1,000  $\mu$ L of the ethanolic supernatant were evaporated to dryness under nitrogen at  $T = 80^{\circ}\text{C}$ , and the residue reconstituted in 200  $\mu$ L diluent (i.e., water containing 0.2% (v/v) Triton X-100 and 0.06% (w/v) cesium chloride). A volume of 20  $\mu$ L, in duplicate, was injected onto the graphite furnace of a Perkin Elmer Model 4110 ZL atomic absorption spectrophotometer (Überlingen, Germany). Platinum peak areas were measured at 265.9 nm. The lower limit of quantitation was established at 0.0300  $\mu\text{g}/\text{mL}$  unbound platinum in plasma. For total platinum analysis, plasma aliquots were accurately sixfold diluted in diluent from which subsequently also aliquots of 20  $\mu$ L were injected onto the graphite furnace. The lower limit of quantitation for total carboplatin-derived platinum was established at 0.200  $\mu\text{g}/\text{mL}$  in plasma.

Urine samples were analyzed, after a fivefold dilution in blank plasma prior to processing, as for total carboplatin-derived platinum as described above.

Aliquots of 25–100  $\mu$ L of peritoneal dialysis samples were evaporated to dryness at  $T = 80^{\circ}\text{C}$  under nitrogen.

The pellets were subsequently dissolved in 100  $\mu$ L blank plasma and further processed as described above for total carboplatin-derived platinum.

#### Paclitaxel analysis

Paclitaxel was quantitated on newly developed and validated methods by liquid chromatography coupled to tandem mass-spectrometric detection (LC–MS/MS), based on a method recently concisely described for docetaxel [11]. Briefly, to 100  $\mu$ L plasma aliquots, 200  $\mu$ L 100 ng/mL docetaxel (10 ng/mL for the sensitive method) in 100% acetonitrile was added. Subsequently, an aliquot of 1 mL *n*-butylchloride was added, where after the samples were vigorously mixed for 10 min. Subsequently, 1 mL aliquots of supernatant, obtained by centrifugation at 18,000g for 10 min, were evaporated under a stream of nitrogen at  $T = 70^{\circ}\text{C}$ . The residues were dissolved in 150  $\mu$ L aliquots of acetonitrile/water/formic acid (40:60:0.1 v/v/v), from which aliquots of 5  $\mu$ L (or 50  $\mu$ L for the sensitive assay) were injected onto an Alltima HP C18 HL 3  $\mu\text{m}$  column ( $50 \times 2.1$  mm internal diameter, Alltech Applied Science, Breda, the Netherlands). The mobile phase, acetonitrile and water with 0.1% (v/v) formic acid, was delivered using a linear gradient setting at a flow rate of 0.2 mL/min with the percentage of acetonitrile changing from 50 to 100% in 1 min. A MicroMass Quatro Micro triple-quadrupole mass spectrometer [Waters Chromatography B.V. (Etten-Leur, The Netherlands)] was used for detection in the positive ion mode. The electrospray ionization was set at 3.8 kV and at the cone voltage at 18 V. The collision energies were set at 13 eV for paclitaxel and 18 eV for docetaxel, with the collision gas (argon) pressure set at 0.004 mbar. The dwell time per channel was set at 0.15 s.

Calibration curves were constructed in the range of 20–1,000 ng/mL (2.00–100 ng/mL for the sensitive assay) by plotting the peak area ratios of paclitaxel (854.3 > 286.2) to the internal standard docetaxel (808.3 > 527.2) versus the known paclitaxel concentration with a 1/concentration weight factor. Urine samples were analyzed after dilution in blank human lithium heparinized plasma prior to processing, while peritoneal dialysis samples were processed non-diluted.

#### Pharmacokinetic data analysis

Individual plasma pharmacokinetic parameters for both total and unbound carboplatin-derived platinum as well as for paclitaxel were estimated using noncompartmental analysis using the software program WinNonLin 5.0 (Pharsight, CA, USA).

## Results

### Clinical

The patient tolerated the treatment well and without severe side-effects or complications. The toxicity of the chemotherapy was limited to uncomplicated bone marrow suppression (see Fig. 1).

No dose reductions of paclitaxel or carboplatin were required during any cycles. Cycles 3 and 5 of the weekly regimen and cycles 5 and 6 of the three-weekly regimen were delayed with one week due to thrombocytopenia CTC grade 2 and or leucocytopenia CTC grade 3. Despite use of erythropoietin, which she already received prior to the start of chemotherapy for her renal anemia, hemoglobin levels decreased to a minimum of 4.2 mmol/L, because of which

red blood cell transfusions were given after the fourth and sixth-weekly cycle and after the first, third and fifth three-weekly cycle.

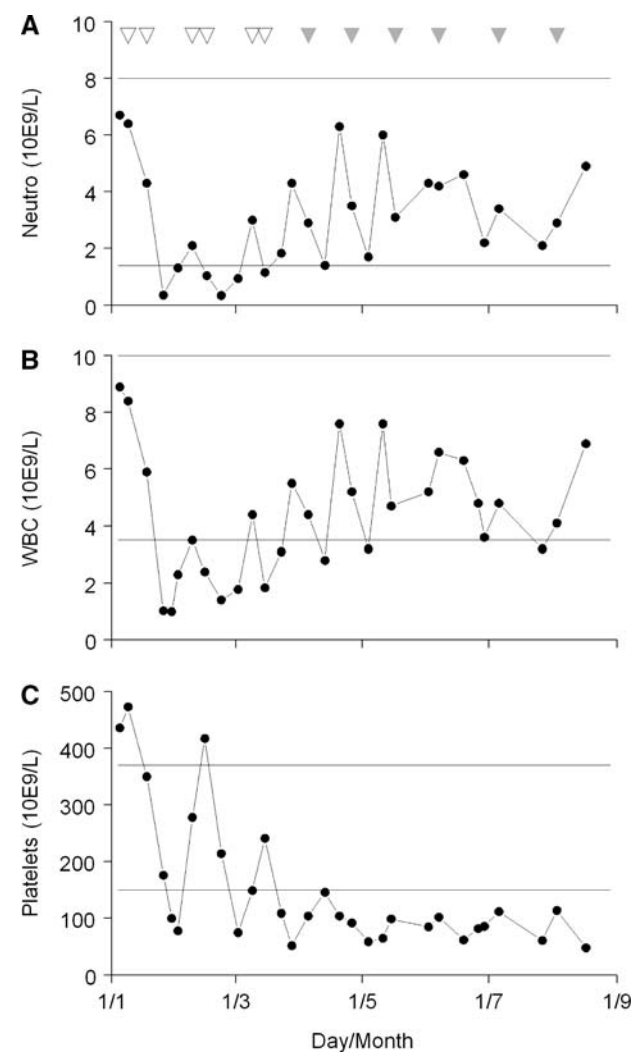
Except for alopecia CTC grade 2, no other non-hematological toxicities were observed. The preexistent CTC grade 1 neurotoxicity remained stable during treatment.

After the induction therapy with six-weekly paclitaxel/carboplatin cycles a partial remission was achieved and at the end of the three-weekly treatment the patient was in a complete clinical remission. Serum CA 125 normalized from 777 to 22 KU/L. After a progression free interval of 17 months the patient had a recurrence, which was once more successfully retreated with weekly paclitaxel and carboplatin.

### Pharmacokinetics

In Table 1 a summary of the pharmacokinetic data of carboplatin-derived total and unbound platinum as well as of paclitaxel are presented, and in Fig. 2 the pharmacokinetic profiles of the compounds in plasma are shown. The plasma pharmacokinetics of the 1- and 3-h infusion of paclitaxel are comparable to those in patients with normal renal function [13, 28, 30]. Paclitaxel was excreted only for approximately 0.15% via the urine and 0.048% via the peritoneal dialysate.

In contrast, the plasma pharmacokinetics of carboplatin-derived platinum were different from historical data [8, 23]. Both unbound and total platinum showed slow clearances of approximately 21 and 10 mL/min, respectively and prolonged half-lives. During the first 24 h after administration, 14–20% of the administered dose of carboplatin was excreted in the peritoneal fluid, with peritoneal clearances in the range of 3.14–4.03 mL/min. Carboplatin was excreted for only 6–8% via the kidneys, with renal clearances in the range of 1.32–1.56 mL/min.



**Fig. 1** Absolute neutrophil (a), white blood cell (b) and platelet (c) count during treatment. The solid lines represent the upper and lower limits of normal values. The triangles indicate the treatment days in the weekly schedule (open symbols) and the three-weekly (closed symbols) schedule

### Discussion

This case study describes the pharmacokinetics of carboplatin and paclitaxel in an adult cancer patient with end-stage renal failure, treated with CAPD. Studies as reported here are of major importance for clinical oncology practice, as (pharmacokinetic guided) clinical studies in patients on substitution therapy for renal failure are scarce.

Paclitaxel, as shown in this report, can be safely administered to patients on CAPD. The observed plasma pharmacokinetics in the studied patient on CAPD were comparable to those in patients with normal renal function [13, 28, 30] and are in agreement with earlier reports of patients with renal failure treated with paclitaxel [1, 18, 19,

**Table 1** Pharmacokinetic data of carboplatin-derived platinum and paclitaxel

Parameter	Course 1	Course 2	Course 9
<i>Carboplatin-derived total platinum</i>			
Target AUC (mg min/mL)	4	4	5
Carboplatin dose (mg) <sup>a</sup>	130	130	150
Platinum dose (mg)	68	68	79
$C_{max}$ ( $\mu\text{g/mL}$ )	4.84	4.98	5.12
$AUC_{0-inf}$ ( $\mu\text{g h/mL}$ )	106	119	137
CL (mL/min)	10.6	9.6	9.6
$T_{1/2}$ (h)	17.6	19.6	19.3
<i>Carboplatin-derived unbound platinum</i>			
$C_{max}$ ( $\mu\text{g/mL}$ )	3.93	3.66	4.67
$AUC_{0-inf}$ ( $\mu\text{g h/mL}$ )	51.6	54.2	67.7
$AUC_{0-inf}$ (mg min/mL) <sup>b</sup>	5.89	6.19	7.73
CL (mL/min)	22.0	20.9	19.4
$T_{1/2}$ (h)	10.5	11.7	10.4
Urine (%)	6.0	6.4	8.0
$CL_{urine}$ (mL/min) <sup>c</sup>	1.32	1.34	1.56
Peritoneal dialysis (%)	14.3	19.3	20.1
$CL_{peritoneal\ dialysis}$ (mL/min) <sup>c</sup>	3.14	4.03	3.37
<i>Paclitaxel</i>			
Dose (mg/m <sup>2</sup> )	90	90	175
Dose (mg)	140	140	270
$C_{max}$ ( $\mu\text{g/mL}$ )	3.71	2.43	3.26
$AUC_{0-inf}$ ( $\mu\text{g h/mL}$ )	6.39	6.07	11.7
CL (mL/min)	365	384	385
$T_{1/2}$ (h)	9.1	9.9	7.8
Urine (%)	0.16	0.15	0.16
$CL_{urine}$ (mL/min) <sup>d</sup>	0.57	0.59	0.60
Peritoneal dialysis (%)	0.047	0.048	0.049
$CL_{peritoneal\ dialysis}$ (mL/min) <sup>d</sup>	0.17	0.18	0.47

<sup>a</sup> Dose calculated according to Eq. 1

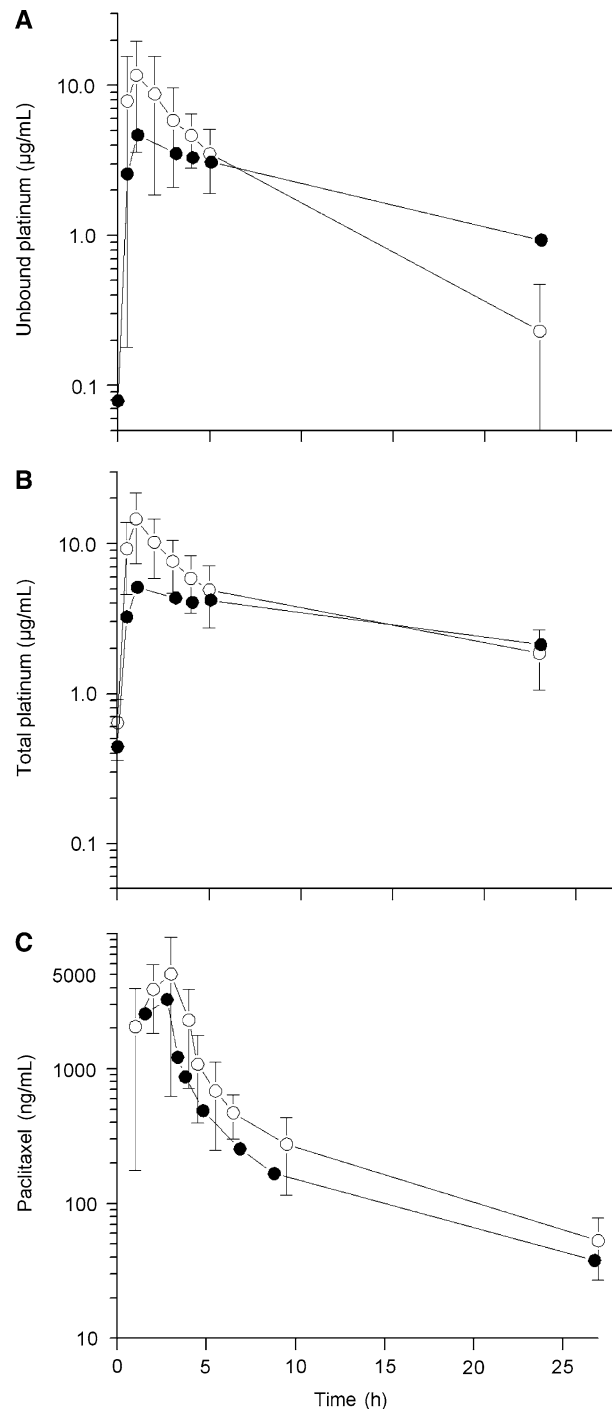
<sup>b</sup> AUC of carboplatin (in stead of platinum) as expressed by Calvert et al. [3]

<sup>c</sup> CL = total amount excreted in urine (or peritoneal dialysate)/AUC unbound carboplatin-derived platinum in plasma

<sup>d</sup> CL = total amount excreted in urine (or peritoneal dialysate)/AUC paclitaxel in plasma

26, 32, 35–37]. As paclitaxel is mainly cleared by biliary secretion, following extensive metabolism by hepatic cytochrome P450 enzymes, and also in patients with normal renal function less than 10% is excreted by the kidneys [21], dose-adjustments in patients with renal dysfunction are not required. In addition, as shown earlier by Gelderblom et al. [14], paclitaxel hardly distributes into the peritoneal cavity, with <1.3% of systemic concentrations found in ascites, which is in agreement with the neglectable clearance of paclitaxel via peritoneal dialysis as reported here.

In contrast to paclitaxel, the pharmacokinetics of carboplatin-derived platinum in plasma were altered compared



**Fig. 2** Plasma concentration time curves of carboplatin-derived unbound (a) and total (b) platinum and of paclitaxel (c). Closed symbols show the data of course nine of the studied patient. Open symbols represent data (mean  $\pm$  2SD) of a reference population of patients with normal renal function treated at our institute ( $n = 12$  for 1 h carboplatin infusion dosed at AUC 5;  $n = 5$  for 3 h paclitaxel infusion dosed at 175 mg/m<sup>2</sup>)

to the pharmacokinetics in patients with normal renal function [8, 23]. The half-lives of total and unbound platinum, as estimated during the first 24 h, were almost



doubled with total and unbound platinum quantifiable up to 7 days after administration. Although the half-life of unbound platinum was doubled, the estimated AUC of unbound carboplatin in the three studied courses was no more than 1.5 times the target AUC. The higher observed AUCs of unbound carboplatin-derived platinum might be a result of a slight overestimation of the GFR value. The GFR value may be overestimated in patients on dialysis as the observed plasma creatinine concentrations are determined by the sum of the urinary and peritoneal dialysis clearances. In contrast to glomerular filtration the clearance via the dialysis is purely gradient driven and depends on the molecular weight of the compound. By setting the GFR value at zero however, the contribution of the peritoneal clearance and the (remaining) residual kidney function would have been neglected and as a result the carboplatin dose would have been underestimated. In addition, the slow clearance and prolonged half-life of carboplatin did not lead to dose limiting toxicities. Peritoneal dialysis cleared 14–20% of the administered dose during the first 24 h, while the kidneys cleared 6–8% in the same time period. In patients with a normal renal function or on hemodialysis, approximately 70% of the dose is cleared via the kidneys or hemodialysate [6, 17, 21, 31]. The observed 20% clearance of carboplatin via peritoneal dialysis in the studied patient is high in contrast to an earlier study of English et al. [12] in which carboplatin was not cleared via peritoneal dialysis, as stated by the authors. The discrepancy might be related to the fact that in our study, a continuous peritoneal dialysis was applied, while in the study of English et al. [12], the peritoneal dialysis was only applied from 5 to 14 h after the start of the carboplatin infusion. Moreover, in the study of English et al. [12], still 30% of the administered carboplatin dose was cleared via the kidneys, in contrast to only 6–8% in our studied patient [12].

In conclusion, paclitaxel and carboplatin can be safely administered to patients with chronic renal failure and on CAPD. Paclitaxel can be administered at therapeutic doses applied to patients with normal renal function. For carboplatin, dose-adjustments are required, however yet the doses can be calculated using Calvert's formula [3].

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