Pharmacokinetics of Paclitaxel and Carboplatin in a Dose-Escalating and Dose-Sequencing Study in Patients With Non-Small-Cell Lung Cancer


Purpose: To investigate the pharmacokinetics and pharmacodynamics of paclitaxel (P) and carboplatin (C) in a sequence-finding and dose-escalating study in untreated non-small-cell lung cancer (NSCLC) patients.

Patients and Methods: Fifty-five chemotherapy-naive patients with NSCLC were entered onto the pharmacokinetic part of a large phase I trial in which P was administered as a 3-hour infusion at doses of 100 to 250 mg/m², and C over 30 minutes at dosages of 300 to 400 mg/m². Patients were randomized for the sequence of administration, first C followed by P or vice versa. Each patient received the alternate sequence during the second and subsequent courses.

Results: The most important hematologic toxicity encountered was neutropenia. Hematologic toxicity was not dependent on the sequence in which P and C were administered, but there was cumulative neutropenia. Nonhematologic toxicities consisted mainly of vomiting, myalgia, and arthralgia. No sequence-dependent pharmacokinetic interactions for the P area under the concentration-time curve (AUC), maximal plasma concentration (Cmax), or time above a threshold concentration of 0.1 µmol/L (P-T ≥ 0.1 µmol/L) were observed. However, there was a significant difference for the metabolite 6a-hydroxypaclitaxel AUC (6OHP-AUC). Higher 6OHP-AUCs were observed when C was administered before P. The mean plasma ultrafiltrate AUC of C (CpUF-AUC) at the dosage of 300 mg/m² for the sequence C→P was 3.52 mg/mL·min (range, 1.94 to 5.83) and 3.62 mg/mL·min for the sequence P→C (range, 1.91 to 5.01), which is not significantly different (P = .55). Of 45 assessable patients, there were five major responders (three complete responders and two partial responders). Four of five responses occurred at dosages above dose level 4 (P 175 mg/m² + C 300 mg/m²). The median survival duration was best correlated with the P dose (4.8 months for doses ≤ 175 mg/m² v 7.9 months for doses ≥ 175 mg/m², P = .07; P-T ≥ 0.1 µmol/L, 4.8 months for < 15 hours v 8.2 months for ≥ 15 hours, P = .06).

Conclusion: There was no pharmacokinetic-sequence interaction between C and P in this study. A clear dose-response relation with respect to response rate and survival was observed. The pharmacokinetic parameter P-T ≥ 0.1 µmol/L was related to improved survival in this study.


Lung cancer is the most common lethal tumor in the Western world, with an increasing incidence among women. Most patients present with inoperable tumors of stage IIIb and stage IV and will die within a few months after diagnosis. Current treatments with available chemotherapeutic regimens show response rates of up to 22% for single agents, with no impact on the median survival duration (4 months) and 1-year survival (± 20%). There is a modest survival benefit in patients treated with a cisplatin-rate containing combination (response rate, 40% to 60%; median survival duration, 10 months). Evidently, new drugs and treatment modalities for this tumor type are warranted.

The taxanes (paclitaxel [P] and docetaxel) are a new and promising class of antitumor agents also used for the treatment of non–small-cell lung cancer (NSCLC). High response rates for the single agents have been reported (20% and 38%), with 1-year survival rates of approximately 40%. Cisplatin is among the most active agents available for the treatment of NSCLC. On the other hand, carboplatin (C) as a single agent produced the best 1-year survival rate with the least toxicity in a five-arm Eastern Cooperative Oncology Group study of cisplatin combinations and analog.7 C is less nephrotoxic, neurotoxic, and emetogenic than the parent compound cisplatin. The main hematologic toxicity for C is thrombocytopenia, and for paclitaxel (P), neutropenia. These partially nonoverlapping...
ping toxicities of C and P, different mechanisms of action, and activity in NSCLC as a single agent made the combination of both drugs attractive for further clinical exploration.

In an attempt to improve the palliation and survival of patients with NSCLC, we combined C with a 3-hour P infusion. Generally, when two drugs are combined, it is important to make allowance for possible drug interactions and schedule dependencies. Several preclinical studies demonstrated a sequence-dependent cytotoxicity for the combination cisplatin-P in vitro, in which the P → cisplatin sequence was more cytotoxic.\(^8\)\(^-\)\(^10\) Rowinsky et al\(^11\) reported a sequence-dependent toxicity for the combination P-cisplatin. Bone marrow toxicity (neutropenia) was more pronounced when cisplatin was given before P as compared with the alternate sequence. Pharmacokinetic monitoring showed that this might be due to a decreased clearance of P, which led to an increased exposure (area under the curve [AUC]) to the drug.\(^11\) Other sequence-dependent interactions have been reported for P and anticancer drugs such as doxorubicin\(^12\) and cyclophosphamide.\(^13\) Since P showed a sequence-dependent interaction with cisplatin, it was believed to be important also to investigate any possible drug and/or sequence interaction with C.

We initiated a phase I dose- and sequence-finding study for the combination of C-P in patients with previously untreated NSCLC. A 3-hour P infusion was chosen, since this schedule may eventually provide an ambulatory form of treatment. The purpose of this study was to investigate whether there is a sequence-dependent interaction between these two drugs by examining the pharmacokinetics and pharmacodynamics of both C and P. This study was part of a multicenter trial coordinated by the European Cancer Centre.

**PATIENTS AND METHODS**

**Patient Selection**

Patients with NSCLC stage IIIb or IV without prior chemotherapy were included in the study. All patients were entered from the three participating institutes of the European Cancer Centre: the Free University Hospital, the Academic Medical Center, and the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, all in Amsterdam. Eligibility criteria included the following: (1) age less than 75 years, (2) Eastern Cooperative Oncology Group performance status ≤ 2, (3) life expectancy greater than 12 weeks, (4) adequate bone marrow function (absolute neutrophil count [ANC] \(\geq 2.5 \times 10^9/L\) and platelet count \(\geq 100 \times 10^9/L\)), (5) serum bilirubin level \(\leq 30 \mu\text{mol/L}\), (6) ALT and AST levels \(\leq 2.5\) times the normal upper limit, (7) serum creatinine level \(\leq 140 \mu\text{mol/L}\); and (8) provision of written informed consent. Results of the clinical part of this study are reported separately.\(^14\)

**Study Design**

Six patients at each dose level were randomized for the administration sequence, either paclitaxel (P) followed by C (P → C) or C followed by P (C → P). The alternate sequence was given for the second and each following course. The starting dose of P was 100 mg/m\(^2\) with 25-mg/m\(^2\) dose increments, with a fixed dose of C (300 mg/m\(^2\)). P was administered as a 3-hour infusion immediately followed by a 30-minute infusion of C (or the alternate sequence) repeated every 4 weeks (Table 1).

**Drug Administration**

Paclitaxel (Taxol; Bristol-Myers Squibb Co, Syracuse, NY) for clinical use was provided as a concentrated sterile solution (6 mg/mL) in a 5-mL vial in a mixture of Cremophor EL and dehydrated alcohol (1:1 vol/vol). This was diluted before use with 1,000 mL 0.9% sodium chloride solution. P concentration in this solution did not exceed 0.6 mg/mL. The drug was administered as a 3-hour continuous intravenous (IV) infusion. Since Cremophor EL may leach plasticizer from solution bags that contain polyvinyl chloride, drug solutions were administered through an IVAC IV administration set with low-sorbing tubing (IVAC Corp, San Diego, CA) or through a 2262 Gemicin 20 IMED primary administration set for nitroglycerin and set emulsion (IMED Corp, San Diego, CA). An IVEX-2 vented filter set (0.22 μm; Millipore, Malsheim, France) was inserted in the infusion line.

Premedication consisted of 20 mg dexamethasone orally 6 and 12 hours before infusion, clemastine 2 mg IV, cimetidine 300 mg IV 30 minutes before P infusion, and antiemetics (depending on the institute: metoclopramide, ondansetron, or granisetron).

C (Paraplatin; Bristol-Myers Squibb) was supplied as a lyophilized product that contained 150 mg C and 150 mg mniol as bulking agent. Immediately before use, the content of each vial was reconstituted with 15 mL water for injection, and the total dose was added to 250 mL dextrose 5%.

**Pharmacokinetics**

**Sampling.** Complete concentration-time curves for both P and C were obtained during the first and second course. Samples for P analysis were collected in EDTA tubes at 21 time points: before initiation of the infusion, 1 and 2 hours after initiation, at the end of infusion, and 5, 10, 15, 30, 45, and 60 minutes and 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 30, and 48 hours postinfusion. C samples were

<table>
<thead>
<tr>
<th><strong>Table 1. Dose Escalation for P and C</strong></th>
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<td><strong>Dose Level</strong></td>
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*Complete pharmacokinetic curves were obtained for P and C in PUF.*
collected in heparin tubes at 12 time points: immediately before the infusion, at the end of infusion, and 0.25, 0.5, 1, 2, 4, 8, 12, 18, 24, and 48 hours after the end of the infusion. Plasma was obtained by immediate centrifugation (5 minutes at 1,500 × g) of the samples. Part of the C-containing plasma was transferred directly to an MPS-1 device equipped with a YMT-30 filter (Amicon Division, W.R. Grace & Co, Danvers, MA) and centrifuged for 10 minutes at 1,500 × g to obtain plasma ultrafiltrate (pUF). Plasma and pUF were stored at −20°C until analysis.

Analysis. P and metabolites were assayed in plasma using a sensitive high-performance liquid chromatographic assay with solid-phase extraction as the sample pretreatment procedure, as previously described.14,15 The major metabolite of P, 6-α-hydroxyplactaxil (6OH), was isolated from the feces of cancer patients treated with P, and was chromatographically purified and structurally identified by mass spectrometry as reported by Sparreboom et al.14 This compound was used as the reference standard for quantitation of this metabolite in plasma. The procedures, including sample pretreatment for the analysis of metabolites, were identical to those used for P.17

Platinum levels were quantified using a validated method based on Zeeman atomic absorption spectrometry, and were recalculated as C concentrations.18

Pharmacokinetic and Pharmacodynamic Analysis

P and 6OH. Postinfusion plasma disappearance curves were modeled using the Kinfit computer program (MW/PHARMEDWARE, Groningen, the Netherlands).20 This nonlinear least-squares, iterative regression program determines slopes and intercepts of the logarithmically plotted curves of multieponential functions and provides a correlation coefficient of the fitted curve. The terminal half-life was calculated from the equation, t1/2(y) = ln 2/λy, where λy is the slope of the terminal gamma phase of the triexponential postinfusion curve. Other pharmacokinetic parameters were calculated by noncompartmental analysis.21 The total area under the plasma concentration-time curve for P (P-AUC0→∞) was calculated using the linear trapezoidal method with extrapolation of the terminal phase to infinity (Ct × λ1), in which Ct is the last measured concentration. The area under the moment curve (P-AUMC0→∞) was also calculated by the trapezoidal rule with extrapolation to infinity ((Ct × λ1 + λ1 × Ct)/λ1) with λ1 as the last time point at which Ct was measured. The mean residence time (P-MRT) was calculated by dividing P-AUMC0→∞ by P-AUC0→∞.

Total-body clearance (P-CL) was calculated by dividing the dose (Dp) by P-AUC0→∞. Volume at steady-state (P-Vss) was calculated with the equation,

\[ P-Vss = \frac{D_p \cdot P-AUC}{P-AUC} - \frac{D_p \cdot T}{2 \cdot P-AUC} \]

where T is the infusion time. Peak plasma concentrations (P-Cmax) are measured values. The time spent above a threshold concentration of 0.1 μmol/L (P-T = 0.1 μmol/L) was derived graphically from the pharmacokinetic curves. The 6OH-P-AUC was determined using the linear trapezoidal rule without extrapolation to infinity.

C. Plasma and pUF platinum concentration-time curves were also modeled with the Kinfit computer program. C AUCs (C-AUCs) were determined on the basis of the fitted curve as the exact integral of the concentration versus time plots from 0 to 48 hours for both plasma and pUF. Other pharmacokinetic parameters such as the half-life values (t1/2α, t1/2β, and t1/2γ), total-body clearance (C-CL), mean residence time (C-MRT), and volume of distribution (C-Vd), were also calculated by the computer program with standard equations.23,24 The maximum concentrations (C-Cmax) were experimental values.

Pharmacodynamics and Statistics

Hematologic toxicity was evaluated as percentage decrease (% D) in granulocyte, WBC, or platelet counts using the following equation:

\[ \% D = \frac{\text{pretreatment value} - \text{value of the nadir}}{\text{pretreatment value}} \times 100\% \]

Hematologic toxicity was assessed by measurement of full blood cell counts with differentials twice weekly.

To investigate whether there was a sequence-dependent interaction for the combination P/C in this study, we compared the regression lines of the sequence P→C versus C→P for, respectively, P-AUC, P-Cmax, P-T = 0.1 μmol/L, 6OH-P-AUC, and C pUF AUC (CpUF-AUC) with the line of identity. We also tested the median values for C pharmacokinetics with a paired Student’s t test for statistical differences.

The influence of patient characteristics on the pharmacokinetic parameters of both P and C was investigated by univariate linear regression and analysis of variance. The following patient characteristics were studied as covariates: body weight, age, and plasma creatinine, alkaline phosphatase (AP), γ-glutamyl transpeptidase (γ-GT), ALT, AST, albumin, and bilirubin levels. The following characteristics were investigated as factors: pleural effusion, performance status, and sex. Furthermore, we tested the effects of C dose and C-AUC on P-AUC, P-T = 0.1 μmol/L, and vice versa. Before analyzing the influence of patient characteristics and C parameters of interest (C dose and CpUF-AUC) on P pharmacokinetic parameters, we normalized the P-AUC to a standard dose. Since P exhibits nonlinear kinetics, we transformed the P-AUC by \( \sqrt{P-AUC} \). After this transformation, a linear equation of dose versus P-AUC was obtained with an equal variance. Survival analysis data were generated by the Kaplan-Meier product for the influences of dose, P-AUC, C-AUC, P-T > 0.1 μmol/L, and 6OH-P-AUC. Comparisons of survival distributions were tested with the Gehan-Wilcoxon test. We used the terms significant and nonsignificant to indicate whether the P value is less than or greater than .05, respectively. The computer programs NCISS (Number Cruncher Statistical System, Kaysville, UT, 1992) and Quattro Pro (Borland International, Scotts Valley, CA, 1992) were used for all calculations.

RESULTS

All comparative results are presented according to a bifactorial design, ie, C → P versus P → C and course 1 versus course 2. Furthermore, the pharmacokinetics were also analyzed in a four-arm manner.

Patient Characteristics

A total of 55 patients were enrolled onto the pharmacokinetic part of the phase I study. During the course of the study, it became clear that no sequence-dependent effect on toxicity was present, and it was then decided to perform the last escalation steps 7, 8, and 9 (Table 1) with
four patients per dose level without randomization with the administration sequence P → C. Characteristics of patients who participated in the pharmacokinetic studies were as follows: median performance status of 1 (range, 0 to 2), mean age of 56 years (range, 38 to 74), 14 women and 41 men, and mean serum creatinine level of $77 \mu\text{mol/L}$ (range, 44 to 144).

**Toxicity**

In all 55 patients, the main hematologic toxicity during the first two courses was neutropenia, with 27% of the assessable courses grade III and 15% grade IV. Mild anemia (grade II) occurred in only 10% of the patients. Thrombocytopenia ($< 100 \times 10^9/\text{L}$) occurred in only one patient, who died of toxicity 1 week after the first cycle (dose level 9, $P = 250 \text{ mg/m}^2 + C = 350 \text{ mg/m}^2$) following an episode of severe leukopenia-neutropenia and thrombocytopenia associated with melena and sepsis. This patient had gross liver involvement and liver function disturbances (ALT level, 98; AST level, 100; and AP level, 588 U/L) before treatment.

Two early deaths occurred at $P = 200 \text{ mg/m}^2$ in combination with $C = 300 \text{ mg/m}^2$ (dose level 5). The first patient, who had a performance status of 2 and was on medication with prednisone and furosemide because of dyspnea, died unexpectedly 1 week after the first cycle. No autopsy was permitted, and treatment-related toxicity could not be excluded as the cause of death. The other patient, in whom tumor regression was already visible 1 week after the first cycle, died a week later due to bowel perforation following necrotic regression. This patient was not considered assessable for response. A third patient died of toxicity 1 week after the first cycle of $P = 250 \text{ mg/m}^2$ in combination with $C = 350 \text{ mg/m}^2$ (dose level 9) following an episode of severe granulocytopenia accompanied by sepsis, thrombocytopenia, and melena. Two other patients died, probably due to disease progression and not to the treatment.$^{14}$

When the first and second cycles were compared, it appeared that neutropenia was more pronounced during the second cycle regardless of sequence. Nausea and vomiting were mild and occurred infrequently with standard prophylactic antiemetic medication. Myalgia and bone pain appeared frequently, and the severities increased with the $P$ dose (especially $\geq 200 \text{ mg/m}^2$). Myalgia was mild in 19% and moderate in 15% of patients treated with doses less than 200 mg/m², whereas for higher doses myalgia was mild in 22%, moderate in 28%, and severe in 9% of the patients. Mild peripheral neurotoxicity was infrequently encountered (12%) for the lower dose levels (< 200 mg/m²), but became more frequent at the higher $P$ doses tested (34%) and was more intense with continuation of the drug. All patients developed alopecia (grade II or III).

**Pharmacokinetics**

$P$. A total of 55 patients participated in the pharmacokinetic study. $P$ pharmacokinetics were studied during the first cycle (n = 53), second cycle (n = 37), third cycle (n = 3), fourth cycle (n = 1), and eighth cycle (n = 1). A total of 37 patients (pharmacokinetic performance during courses 1 and 2) were assessable for the sequence interaction between $P$ and $C$. The other 18 patients had no pharmacokinetic monitoring during the second course, due to inadvertently receiving the same sequence during both cycles (n = 2), a severe hypersensitivity reaction during the second cycle (n = 1), unexpected death (n = 5), patient refusal (n = 1), deterioration of performance status (n = 2), and closure of the sequence interaction study (n = 7). $P$ demonstrated a clear nonlinear kinetic behavior, as shown by the exponential relationship between the dose and AUC and an increase in variation for the higher dosages (Fig 1).

The plasma pharmacokinetics of $P$ could be described for the postinfusion period by a three-exponential equation.$^{15}$ The prolonged and greater exposure to $P$ for the higher dose levels is illustrated in Fig 2 by three typical patient concentration-time curves for $P$ at three different dose levels (100, 200, and 250 mg/m²). The mean phar-

![Fig 1. Relationship between $P$ dose and $P$-AUC. {---} {---} Regression curve.](image-url)
macokinetic parameters for P and the major metabolite 6OHP are listed in Table 2.

Plasma disappearance curves for 6OHP show monoexponential or biexponential phases for lower P doses and triexponential phases for higher P doses (Fig 3). The mean 6OHP-AUCs increased 35-fold from 0.16 μmol/L at P 100 mg/m² to 5.69 μmol/L at P 250 mg/m². This nonlin-

earity became most apparent at P doses above 150 mg/m².

The mean 6OHP-AUC-P-AUC ratio increased eightfold from 1:32.5 for the 100-mg/m² dose level to 1:4 for the 250-mg/m² dose level.

Comparison between the two sequences showed that the regression lines did not differ significantly from the line of identity (P-Cmax-Cp = 1.02 ± 0.04 P-Cmax-Cp, r = .91; P-AUCP-Cp = 0.92 ± 0.03 P-AUCp-Cp, r = .90 [Fig

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Table 2. Pharmacokinetics of P and 6OHP (mean ± SD)

<table>
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<tr>
<th>Cohort</th>
<th>Dose (mg/m²)</th>
<th>Sequence</th>
<th>No.</th>
<th>P &gt; 0.1 (μmol/L)</th>
<th>C∞ (μmol/L)</th>
<th>AUC∞ (μmol L-h)</th>
<th>h1/2 γ (h)</th>
<th>Cl (L/h)</th>
<th>Vd (L)</th>
<th>6OHP-AUC (μmol L-h)</th>
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<tbody>
<tr>
<td>1 P100</td>
<td>C-P</td>
<td>6</td>
<td>7.6 ± 3.6</td>
<td>1.5 ± 1.0</td>
<td>5.8 ± 3.5</td>
<td>24.9 ± 13.1</td>
<td>43.1 ± 15.4</td>
<td>506 ± 216</td>
<td>0.19 ± 0.19</td>
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<tr>
<td>2 C300</td>
<td>P-C</td>
<td>6</td>
<td>6.3 ± 1.1</td>
<td>1.2 ± 0.4</td>
<td>4.6 ± 1.0</td>
<td>24.1 ± 27.6</td>
<td>44.4 ± 13.1</td>
<td>633 ± 796</td>
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<td>C-P</td>
<td>8</td>
<td>8.7 ± 2.0</td>
<td>2.1 ± 0.6</td>
<td>6.8 ± 1.2</td>
<td>14.0 ± 8.5</td>
<td>37.3 ± 8.2</td>
<td>268 ± 167</td>
<td>0.12 ± 0.07</td>
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<td>P-C</td>
<td>6</td>
<td>9.7 ± 4.3</td>
<td>2.2 ± 1.2</td>
<td>7.0 ± 2.2</td>
<td>17.8 ± 12.9</td>
<td>40.1 ± 14.7</td>
<td>321 ± 201</td>
<td>0.23 ± 0.15</td>
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<td>11.5 ± 2.8</td>
<td>2.5 ± 0.6</td>
<td>8.4 ± 1.8</td>
<td>9.1 ± 1.9</td>
<td>37.0 ± 7.7</td>
<td>181 ± 50</td>
<td>0.24 ± 0.16</td>
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<td>P-C</td>
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<td>12.6 ± 4.4</td>
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<td>15.2 ± 8.8</td>
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<td>C-P</td>
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<td>18.1 ± 5.4</td>
<td>3.8 ± 1.1</td>
<td>14.7 ± 4.4</td>
<td>18.0 ± 18.6</td>
<td>28.7 ± 7.0</td>
<td>282 ± 262</td>
<td>0.36 ± 0.16</td>
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<tr>
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<td>P-C</td>
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<td>14.0 ± 3.6</td>
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<td>12.3 ± 3.1</td>
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<td>35.1 ± 12.4</td>
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<td>17.5 ± 3.8</td>
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<td>24.3 ± 8.0</td>
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<td>149 ± 52</td>
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</tbody>
</table>
4): \[ P\cdot T \cong 0.1 \mu\text{mol/L}_{C-\text{P}} \cong 0.87 \pm 0.05 \text{ P-T} \cong 0.1 \mu\text{mol/L}_{C-\text{P}}, \ r = .55; \] \( P\cdot \text{Cl}_{C-\text{P}} = 1.00 \pm 0.04 \text{ P-Cl}_{C-\text{P}}, \ r = .64). \) However, there was a significant difference for the metabolite \( (60\text{HP-AUC}_{C-\text{P}} = 0.58 \pm 0.08 \text{ 60HP-AUC}_{C-\text{P}}, \ r = .64). \) There is no indication that the pharmacokinetic parameters of interest between course 1 and course 2 (indicated by subscripts 1 and 2, respectively) were different, although a minor deviation for \( \text{P-T} \cong 0.1 \mu\text{mol/L} \) occurred \( (P\cdot \text{max}_{2} = 0.97 \pm 0.03 \text{ P-\text{max}_{1}}, \ r = .91; \text{P-AUC}_{2} = 0.95 \pm 0.03 \text{ P-AUC}_{1}, \ r = .90; \text{P-T} \cong 0.1 \mu\text{mol/L}_{2} = 0.85 \pm 0.05 \text{ P-T} \cong 0.1 \mu\text{mol/L}_{1}, \ r = .55; \text{P-Cl}_{2} = 0.98 \pm 0.04 \text{ P-Cl}_{1}, \ r = .67; \text{60HP-AUC}_{2} = 0.86 \pm 0.13 \text{ 60HP-AUC}_{1}, \ r = .63). \) Data for the slopes of the regression lines analyzed in a four-arm manner are listed in Table 3.

No significant sequence-independent pharmacokinetic drug interaction between P and C could be found. We observed approximately a 17% decrease in \( \text{P-AUC} (24.36 \pm 7.42 \text{ v} 20.2 \pm 2.79, P = .11), \) a 40% decrease in \( \text{60HP-AUC} (1.71 \pm 1.6 \text{ v} 0.98 \pm 0.26, P = .13), \) and a 20% decrease in \( \text{P-T} \cong 0.1 \mu\text{mol/L} (21.9 \pm 6.9 \text{ v} 17.3 \pm 3.2, P = .07) \) when the C dose was escalated from 300 mg/m² (dose level 6) to 350 mg/m² (dose level 7) with a fixed P dose of 225 mg/m². None of these differences reached the level of significance.

Several patients in this study had a marked change in routine biochemical values for liver function between two pharmacokinetic courses or used other drugs, which may influence the distribution, excretion, or metabolism of P or C. Fifteen of 37 assessable patients for the sequence interaction study had abnormal laboratory tests (AP level \( \geq 120 \text{ U/L}, \gamma-GT \text{ level} \geq 50 \text{ U/L}, \text{ALT level} \geq 35 \text{ U/L}, \text{or AST level} \geq 35 \text{ U/L}). \) Six of 15 patients had a major difference in the routine biochemical values for liver function between courses 1 and 2. These six patients had a marked difference in the pharmacokinetic profile between both courses. A change in the concomitant medication may also lead to a change in pharmacokinetic behavior. One patient developed generalized epileptic seizures at 3.5 weeks after receiving the first course of P-C. The patient underwent surgery and irradiation therapy for a large solitary brain metastasis. Six weeks later, the patient continued the P-C chemotherapy with diphtoainone (500 mg 100 mg) support. Although there was a marked increase in AP and \( \gamma-GT \) levels from course 1 to course 2, there was a decrease in all pharmacokinetic parameters. Another patient experienced grade II neuromuscular symptoms of severe muscle cramps of the upper legs, upper arms, and cheeks. Because of the muscle cramps, the patient self-administered relatively large doses of oxazepam, temazepam, and lorazepam in combination with paracetamol/codeine without medical supervision. This patient had a remarkable change in the pharmacokinetic parameters of interest (P-AUC decreased, \( \text{P-T} \cong 0.1 \mu\text{mol/L} \) decreased, and \( \text{60HP-AUC} \) decreased, with an increase in \( \text{CpUF-AUC}). \) It must be noted that the hematologic toxicity for this patient was decreased (course 1: WBC count, 1,400/\muL, and ANC, 140/\muL, for 4 days accompanied by a fever of 39.5°C; course 2: WBC count, 2,400/\muL, and ANC, 20/\muL, for 4 days with no fever) during the second course, but the patient developed benign paroxysmal vertigo during the second course. After reduction of the benzodiazepine medication, hematologic toxicity worsened during the fourth course.

### Table 3. Comparison of the Slopes of the Regression Line \( (a = x + b) \) for the Sequence C-P (cycle 1) Versus C-P (cycle 2) and the Sequence P-C (cycle 1) Versus C-P (cycle 2)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>XY</th>
<th>P-C 1</th>
<th>C-P 1</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{P-C}_{\text{max}} )</td>
<td>C-P,1</td>
<td>1.02 ± 0.04</td>
<td>.96</td>
<td></td>
</tr>
<tr>
<td>( \text{P-AUC}_{\text{max}} )</td>
<td>C-P,1</td>
<td>0.86 ± 0.06</td>
<td>.87</td>
<td></td>
</tr>
<tr>
<td>( \text{P-T} \cong 0.1 \mu\text{mol/L} )</td>
<td>C-P,1</td>
<td>0.71 ± 0.09</td>
<td>.33</td>
<td></td>
</tr>
<tr>
<td>( \text{P-Cl} )</td>
<td>C-P,1</td>
<td>0.99 ± 0.09</td>
<td>.24</td>
<td></td>
</tr>
<tr>
<td>( \text{60HP-AUC} )</td>
<td>C-P,1</td>
<td>0.80 ± 0.03</td>
<td>.99</td>
<td></td>
</tr>
<tr>
<td>( \text{CpUF-AUC} )</td>
<td>C-P,1</td>
<td>1.02 ± 0.05</td>
<td>.59</td>
<td></td>
</tr>
</tbody>
</table>

Fig 4. Relationship between P-AUC (\( \mu\text{mol/L} \cdot \text{h} \)) for the sequence C followed by P and the sequence P followed by C. (— — —) Line of identity, (— — —) Regression line.
and the patient nearly died of septic shock (course 4: WBC count, 1,000/µL, and ANC, 50/µL, with fever, tachycardia, and hypotension). The benign paroxysmal position vertigo slowly disappeared during the third and fourth courses.

C. The plasma pharmacokinetics of total platinum could be best described with a standard open three-compartment model. Overall, the mean pharmacokinetic parameters for the P → C versus C → P sequence normalized for 300 mg/m² were as follows: C-AUC_{P→C}, 6.31 ± 1.92 mg/mL·min, and C-AUC_{C→P}, 6.22 ± 1.52 mg/mL·min (P = .79); C-Cl_{P→C}, 6.0 ± 1.8 L/h, and C-Cl_{C→P}, 5.6 ± 1.9 L/h (P = .28); and t_{1/2γP→C}, 6.5 ± 8.6 days, versus t_{1/2γC→P}, 7.5 ± 12.6 days (P = .64). Maximum plasma concentrations (C_{max}) were achieved at the end of infusion, and were identical to the C_{max} in pUF (Table 4). Pharmacokinetics of ultrafilterable platinum fitted optimally with a standard open two-compartment model. The sequence P → C versus C → P resulted in the following: CpUF-C_{max,P→C}, 86.8 ± 18.1 µmol/L, and CpUF-C_{max,C→P}, 86.5 ± 15.9 µmol/L (P = .92); CpUF-AUC_{P→C}, 3.6 ± 0.8 mg/mL·min, and CpUF-AUC_{C→P}, 3.6 ± 0.7 mg/mL·min (P = .94); CpUF-Cl_{P→C}, 9.5 ± 2.4 L/h, and CpUF-Cl_{C→P}, 9.6 ± 2.2 L/h (P = .88); and t_{1/2βP→C}, 2.7 ± 1.5 hours, and t_{1/2βC→P}, 5.11 ± 11.29 hours (P = .16).

Comparison between the two sequences C → P versus P → C and between course 1 versus course 2 showed no significant differences (r = .72; CpUF-AUC_{P→C}, 0.98 × CpUF-AUC_{C→P}, r = .71; CpUF-AUC_{2→1}, 1.03 × CpUF-AUC_{1→2}; Fig 5).

The 24-hour urinary excretion of C (measured as total platinum) was measured in 17 patients. The mean level excreted was 75% of the administered dose (range, 42% to 115%).

Analysis of Variance

Univariate analysis showed that higher bilirubin levels and age were associated with higher P-AUC levels.
(Table 5). Higher P dose, age, and elevated γ-GT levels were associated with prolonged circulating P concentrations (P-T ≥ 0.1 μmol/L). 6OHP levels were higher in patients with liver dysfunction (Table 5). For all pharmacokinetic parameters, there were no significant relationships with albumin levels. A dose-dependent influence of routine biochemical values (eg, AP and γ-GT levels) on the pharmacokinetic parameters of P was observed. At the P dose of 225 mg/m², the influence of an increased AP level on P-AUC (24.04 ± 6.53 vs 19.9 ± 4.13, P = .05) was more pronounced than the influence of an elevation of γ-GT level (P-AUC, 22.96 ± 6.27 vs 20.58 ± 4.87, P = .27). There was a modest but significant correlation between CpUF-AUC and creatinine clearance (r = -.52, P < .0001) and age (r = .34, P = .0008) (Table 5).

There were no clear correlations between the percent decrease in platelet counts and CpUF-AUC (Fig 6). Both the percent decrease in WBC count and ANC were more pronounced than could be expected on the P-T ≥ 0.1 μmol/L as compared with the results of our previously reported study.{}^{15} This is a remarkable phenomenon, because in the current study patients were chemotheraphy-naïve, whereas in the former study patients were heavily pretreated with platinum analogs (Fig 7).

**Survival Analysis**

Six of 45 assessable patients who participated in this phase I trial are still alive (57+, 65+, 71+, 78+, 84+, and 99+ weeks). There were five major responders (three complete responders and two partial responders) and two minor responders. The median survival duration was 23.5 weeks. The 1-year survival rate was 20%. In analysis of the influence of pharmacokinetic parameters on survival time, we found a positive correlation with P dose, C dose, P-T ≥ 0.1 μmol/L, P-AUC, and CpUF-AUC. When the dose of P was ≥ 175 mg/m², the median survival duration increased from 21 weeks to 34 weeks (P = .06; Fig 8). The estimated 1-year survival rate for P doses ≥ 175 mg/m² is 25% (95% confidence interval, 8% to 42%), whereas the 1-year survival rate for P doses less than 175 mg/m² is 11% (95% confidence interval, 0% to 24%). Of all the investigated pharmacokinetic parameters, P-T ≥ 0.1 μmol/L showed the highest correlation with the median survival. When P-T ≥ 0.1 μmol/L exceeded 15 hours, the median survival duration increased to 35 weeks, compared with 21 weeks for the shorter exposures (P = .05; Fig 9). The estimated 1-year survival rate for P-T ≥ 0.1 μmol/L ≤ 15 hours is 28% (95% confidence interval, 7% to 48%), and the 1-year survival rate for P-T ≥ 0.1 μmol/L less than 15 hours is 12% (95% confidence interval, 0% to 25%).

**DISCUSSION**

Exciting results have been reported recently for the combination cisplatin-P (24-hour infusion) in untreated suboptimally debulked ovarian cancer patients.{}^{23} Cisplatin-based combinations have also shown a modest but definite improvement in survival in the treatment of advanced NSCLC; however, the marked toxicity is a major

<p>| Table 5. AUC, P-T ≥ 0.1 μmol/L, 6OHP-AUC, and CpUF-AUC in Relation to Patient Characteristics |
|---------------------------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>P-AUC (μmol/L·h)</th>
<th>P-T ≥ 0.1 μmol/L·h</th>
<th>6OHP-AUC (μmol/L·h)</th>
<th>CpUF-AUC (mg/mL·min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.38</td>
<td>.0028</td>
<td>.44</td>
<td>.0006</td>
</tr>
<tr>
<td>Weight</td>
<td>.12</td>
<td>.37</td>
<td>.20</td>
<td>.14</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>-.03</td>
<td>.83</td>
<td>-.22</td>
<td>.09</td>
</tr>
<tr>
<td>P dose (mg)</td>
<td>.68</td>
<td>&lt;.00001</td>
<td>.44</td>
<td>.0008</td>
</tr>
<tr>
<td>P dose (mg/m²)</td>
<td>.61</td>
<td>&lt;.00001</td>
<td>.02</td>
<td>.31</td>
</tr>
<tr>
<td>P-AUC (μmol/L·h)</td>
<td>.70</td>
<td>&lt;.0001</td>
<td>.12</td>
<td>.25</td>
</tr>
<tr>
<td>P-T ≥ 0.1 μmol/L (h)</td>
<td>.60</td>
<td>&lt;.0001</td>
<td>.09</td>
<td>.41</td>
</tr>
<tr>
<td>60HP-AUC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C dose (mg)</td>
<td>-.15</td>
<td>.25</td>
<td>.29</td>
<td>.02</td>
</tr>
<tr>
<td>C dose (mg/m²)</td>
<td>-.29</td>
<td>.02</td>
<td>.26</td>
<td>&lt;.04</td>
</tr>
<tr>
<td>CpUF-AUC</td>
<td>.03</td>
<td>.84</td>
<td>.14</td>
<td>.28</td>
</tr>
<tr>
<td>AP</td>
<td>.06</td>
<td>.63</td>
<td>.14</td>
<td>.29</td>
</tr>
<tr>
<td>γ-GT</td>
<td>.005</td>
<td>.97</td>
<td>.35</td>
<td>.007</td>
</tr>
<tr>
<td>ALT</td>
<td>.04</td>
<td>.79</td>
<td>.29</td>
<td>.03</td>
</tr>
<tr>
<td>AST</td>
<td>-.05</td>
<td>.72</td>
<td>.19</td>
<td>.16</td>
</tr>
<tr>
<td>Albumin</td>
<td>-.07</td>
<td>.57</td>
<td>-.02</td>
<td>.9</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>.32</td>
<td>.01</td>
<td>.43</td>
<td>.0007</td>
</tr>
</tbody>
</table>
Although we did not observe a sequence-dependent interaction between P and C increased metabolite concentrations of 6OHP were observed when C was administered before P. Statistical analysis showed that the two groups were not balanced for routine liver enzyme tests, although they fulfilled the eligibility criteria. More patients with relatively higher AP, γ-GT, ALT, and AST levels were entered onto the C → P arm. When these patients were omitted in the analysis, there was no relevant pharmacokinetic sequence interaction left ($r = .77$, 6OHP-AUC$_{P→C}$, 0.86 ± 0.06 6OHP-AUC$_{C→P}$).

Another important observation from this study is that no clear difference was found between the pharmacokinetics of P during the first and second courses.

Although there was no sequence-dependent pharmacokinetic interaction found in this study design, it is still possible that a pharmacokinetic interaction between both drugs occurs, but with no sequence dependency in the manner we studied it. However, the pharmacokinetic data for P are well in agreement with previously reported studies.15,27-29 P-AUCs for P 175 mg/m$^2$ in the present study were 13.4 ± 3.8, versus 14.4 ± 3.2 ($P = .38$) in our previous study.15 The same holds true for the pharmacokinetic parameters in our study of high-dose P (250 mg/ m$^2$) in anthracycline-resistant breast cancer.27 P-AUCs in the former study were 27.1 ± 8.6, versus 23.8 ± 12.8 ($P = .59$) in the present study. However, a complete comparison between these studies is not possible, because a different patient group was studied with no prior exposure to chemotherapeutic agents.

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**Fig 6. Relationship between CpUF-AUC and the percentage decrease in platelets.**

The relatively mild toxicity profile of C and the reduced hematologic toxicity for the shorter P infusions make the P-C combination attractive for further evaluation in NSCLC.

The observation that the toxicity and pharmacokinetics for the combination cisplatin-P are sequence-dependent raised the question as to whether this is also true for the combination C-P, whereby P is administered as a 3-hour infusion. A bifactorial design was selected as the most efficient way to address this question. However, the small number of patients accrued at each dose level makes the four-arm approach for analysis of the data difficult and less reliable.

Results from the present study indicate that there are no sequence-dependent toxicities or sequence-dependent pharmacokinetic interactions for this combination. The reduced P clearance in the cisplatin-P sequence has been attributed to inhibition by cisplatin of cytochrome P-450-dependent P-metabolizing enzymes. C does not modulate cytochrome P-450 enzymes, which may explain the lack of sequence-dependent interaction in the present study. The lack of any sequence-dependent hematologic toxicity might also be related to the cell-cycle specificity of both drugs. Cisplatin reacts immediately with DNA, forming interstrand and intrastrand cross-links and leading to an S-phase arrest, whereas C has a delayed activity with regard to the formation of platinum-DNA adducts (6 to 12 hours). This phenomenon may be crucial, especially when both drugs are administered within a 4-hour period. The cells viable to P will enter the G2/M phase and will be less sensitive to C than cells in the other cell-cycle phases.

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**Fig 7. Percent decrease in ANC versus duration of P concentration above a threshold of 0.1 μmol/L. Curve represents the fitted historical $E_{max}$ model. Dose levels: 100 mg/m$^2$ (△), 125 mg/m$^2$ (○), 150 mg/m$^2$ (+), 175 mg/m$^2$ with 200 mg/m$^2$ (△), and 225 mg/m$^2$ with 250 mg/m$^2$ (●). (-----) $E_{max}$.**
Previous pharmacokinetic studies showed a disproportionately increase in both $C_{\text{max}}$ and AUC with higher doses of P administered as a 3-hour infusion, which indicates that saturation occurs for both elimination and tissue-distribution processes.\textsuperscript{15,28,29} This is in accordance with the observation in this study, and the nonlinearity is even more pronounced for 6OHP. An increased 6OHP-AUC:P-AUC ratio (1:32.5 to 1:4) with P dose is in agreement with this observation. Clinical data on the pharmacokinetics of 6OHP are scarce, and were only described for the higher P doses (225 and 250 mg/m$^2$). The reported 6OHP-AUCs for the 225-mg/m$^2$ dose level were 3.22 ± 1.7 μmol/L·h\textsuperscript{28} (N = 15, extrapolated to infinity), versus 1.36 ± 1.2 μmol/L·h (n = 24, measured AUC) in this study. For the 250-mg/m$^2$ P dose, 6OHP-AUCs were 1.56 ± 1.03 μmol/L·h\textsuperscript{27} (n = 9, measured AUC), versus 5.69 ± 6.55 μmol/L·h (n = 4, measured AUC) herein. However, the number of patients is small with a large interpatient variation, making a comparison of different studies difficult. Approximately 26% of the administered P dose is converted to 6OHP.\textsuperscript{30} It can be expected that the volume of distribution of this more polar metabolite is smaller than for P, which results in higher plasma concentrations. The observed lower plasma concentrations may indicate a fast elimination of this compound into bile and feces. On the other hand, at higher dose levels, the nonlinear pharmacokinetics of this compound become more apparent.

The more than 35-fold (0.16 to 15 μmol/L·h) difference in 6OHP-AUCs between the lowest (100 mg/m$^2$) and highest (250 mg/m$^2$) P doses and the more than proportional increase for the $C_{\text{max}}$ of this compound indicate that both the distribution and consecutive metabolic pathways of this compound are saturated. The observed phenomenon is in agreement with the findings reported by Gianni et al.\textsuperscript{28} They reported that measurable metabolite concentrations represent an overflow of this compound into the circulation, especially in situations of relative saturation or blockade of biliary elimination. An increased
P:60HP ratio (from 1:32.5 to 1:4) with increasing dose and higher 60HP-AUCs in patients with elevated γ-GT and AP levels, an indication of biliary tract disease, are in accordance with the overall hypertension.

Treatment with the combination C-P was well tolerated. However, at the lowest dose level, more pronounced neutropenia occurred than could be expected on the positive correlation between the P-T ≥ 0.1 μmol/L and the bone marrow suppression according to a sigmoidal E_{max} model reported in our previous study, when P was given as a single agent.\textsuperscript{15}

A pharmacokinetic explanation for the increased neutropenia at the lowest dose level cannot be given. A 50% decrease in leukocytes and neutrophils occurred in heavily pretreated patients when the P-T ≥ 0.1 μmol/L was approximately 11 and 15 hours, respectively.\textsuperscript{15} Although the P-T ≥ 0.1 μmol/L in the first dose level was only 7 hours, the percentage decrease in neutrophils was greater than 50%. At higher dose levels, no significant differences could be observed from the earlier described equation.

The myelosuppression involved only leukocytes and not platelets. In general, thrombocytopenia (grade I to III) occurs at C doses of 300 to 400 mg/m², especially in combination regimens.\textsuperscript{7,34} Several other investigators reported for the P-C combination a reduced platelet toxicity at conventional C doses, and even at higher doses (up to 600 mg/m²).\textsuperscript{32-34} However, the underlying mechanism for this phenomenon is not clear yet.

For the reduced platelet toxicity, a pharmacokinetic but sequence-independent explanation seems likely, because most patients (65%) had a C-AUC less than 4 mg/mL·min, which is generally not associated with thrombocytopenia.\textsuperscript{7,34} On the other hand, CpUF-AUCs up to 6.5 mg/mL·min were also obtained in some patients, with no thrombocytopenia. Such CpUF-AUC values are usually accompanied by significant thrombocytopenia. Kearns et al\textsuperscript{32} reported an AUC_{50} value (the AUC by which a 50% decrease in platelets is elicited) of 2.04 mg/mL·min for single-agent C, which increased to 3.42 mg/mL·min when C was administered in combination with P (24-hour infusion). In our study, a 50% decrease in platelets, obtained by a sigmoidal E_{max} model, could not be determined because most AUCs were accompanied by less than a 50% decrease in platelets.

Several speculations concerning the platelet-protective properties can be made, as follows: (1) the release of hematopoietic growth factors (eg, granulocyte-macrophage colony-stimulating factor) induced by P in the bone marrow prohibit severe myelosuppression,\textsuperscript{35} (2) the vehicle Cremophor EL has a protective capacity for hematopoietic regeneration,\textsuperscript{36} and (3) antagonistic intracellular interactions\textsuperscript{19,37} are involved.

Although the hematologic toxicity of the combination C and P was milder than expected, it must be noted that at the highest P dose (250 mg/m²), lethal toxicity was encountered in a patient with gross liver involvement and liver enzyme disturbances (increased ALT, AST, AP, and γ-GT levels), for which reason the study was discontinued. Pharmacokinetic analysis showed a high P-AUC (44 μmol/L·h), prolonged P-T = 0.1 μmol/L (35.5 hours), and high 60HP-AUC (15 μmol/L) with normal C levels at the given dose.

Although antagonistic properties for the platelet toxicity have been observed, antagonism with regard to efficacy has not been observed for this combination in NSCLC and ovarian cancer. Response rates up to 62% with a 1-year survival rate greater than 50% were reported for the combination P and C in NSCLC.\textsuperscript{38} In this study, P was given as a 24-hour infusion with a C dose of 7.5 mg/mL·min. The median survival duration in our study was the same as reported for P as a single agent\textsuperscript{14} (23.5 weeks), with a survival benefit (median survival duration, 31.3 weeks) for patients with stable disease, and more than 47 weeks for patients who responded to therapy. The same results were reported for a 3-hour P infusion with a C-AUC of 6 mg/mL·min.\textsuperscript{39} Of 45 assessable patients who were entered onto the pharmacokinetic part of the trial, nine survived longer than 1 year (20%). The most important prognostic factor for survival in NSCLC is the stage of disease. Only a minor impact on overall survival has been reported for patients who receive chemotherapy.\textsuperscript{1}

A clear dose-response relationship with respect to response rate and survival was observed. It appears that a minimum P dose of 175 mg/m² when administered as a 3-hour infusion is needed to achieve clinically meaningful responses in advanced NSCLC. At this dose level, the nonlinearity of P becomes more apparent, as shown by the more than proportional increase in the AUC and C_{max} and the increase in interpatient variability. Due to the nonlinear pharmacokinetic behavior of P, prolonged circulating P levels and prolonged tumor exposure could be expected. An interesting finding from this study is that the P-T ≥ 0.1 μmol/L greater than 15 hours is positively related to improved survival. This observation may have profound clinical consequences for the infusion duration, and warrants further confirmation in other studies.

Several preclinical studies described a schedule-dependent cytotoxicity in NSCLC cell lines, which supports the importance of prolonged exposure.\textsuperscript{40,41} It could indi-
cate that prolonged infusions of P improve the response rate and overall survival.

In conclusion, the combination P/C is well tolerated and feasible for outpatient treatment. No sequence-dependent effects on the pharmacokinetics of both C and P were observed, or on the toxicity, when P was administered as a 3-hour infusion. Whether a sequence-dependent effect would exist when P is administered as a 24-hour infusion in combination with C is not known. However, there is a reduced platelet toxicity with a tendency to more pronounced neutropenia. Pharmacokinetic monitoring in subsequent studies is pivotal, and may teach us more about the indications we found for a positive relation between survival and P-T ≥ 0.1 μmol/L.

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