Pharmacokinetics of Carboplatin with and without Amifostine in Patients with Solid Tumors

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ABSTRACT

We showed previously that amifostine (WR 2721; Ethyl), a protector against carboplatin-induced toxicities, changed the pharmacokinetics of carboplatin in tumor-bearing nude mice. In the present study, the influence of amifostine on the pharmacokinetics of carboplatin was studied in patients when carboplatin was given in combination with three doses of amifostine, administered just before the carboplatin infusion and 2–4 h thereafter. Compared with a control group of patients who received carboplatin alone, the patients receiving the combination had a longer final half-life of ultrafilterable platinum species (5.0 h versus 3.5 h in patients with a normal creatinine clearance ([Ccr] > 80 ml/min); 5.6 h versus 4.2 h in those with an impaired renal function ([Ccr] < 80 ml/min)). This might be caused by an influence of amifostine on the renal clearance of carboplatin as suggested by a transient increase in serum creatinine levels 24 h after treatment in the patients receiving the combination (mean ± SD: 34.1% ± 17.2% versus −1.8% ± 16.5% in patients treated with carboplatin alone). The impact of these changes on the area under the concentration-time curves of the ultrafilterable platinum species was hardly noticeable in patients with a normal renal function but led to a significant increase in patients with an impaired renal function (395 ± 59 μmol/l/h versus 280 ± 62 μmol/l/h in patients receiving carboplatin alone). The clinical relevance of this influence is unclear, although theoretically it may result in an increase in the efficacy of carboplatin, as has been observed in tumor-bearing nude mice.

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INTRODUCTION

Carboplatin [cis-diammine(1,1-cyclobutanedicarboxylato) platinum(II)] is used in the treatment of several solid tumors. It has demonstrated less nephrotoxicity, neurotoxicity, and ototoxicity in comparison to the parent compound cisplatin [cis-diaminedichloroplatinum(II)], whereas it appears to have similar antitumor activity in several tumor types. Its dose-limiting toxicity is myelosuppression, especially thrombocytopenia. Modulating agents are under investigation to reduce these Pt³− induced toxicities and thus to improve their therapeutic efficacy.

Amifostine [S-2-(3-aminopropylamino)ethylphosphorothioic acid; WR 2721; Ethylol] was initially developed as a radioprotector. At present, it is under investigation as an attractive chemoprotective agent. Preclinical and clinical studies have shown that amifostine selectively protects against Pt-induced side effects without reducing the antitumor activity (1–3). This selective protection is thought to be based on the preferential formation and uptake of the active metabolite of amifostine, the aminothiol WR 1065, in nontumor tissues (4, 5).

In some preclinical studies, the combination of amifostine with a cytostatic agent seemed to be more active than treatment with the cytostatic agent alone (6–9). We found that amifostine increased the efficacy of carboplatin in nude mice bearing OVCAR-3 xenografts. In addition, treatment with amifostine resulted in higher Pt concentrations in plasma, normal tissues, and tumor tissue in these mice (9).

The aim of this study was, therefore, to investigate whether amifostine also influenced the pharmacokinetics of carboplatin in patients. To this purpose, the pharmacokinetics of carboplatin were studied both in patients who received carboplatin plus amifostine within the context of a Phase I trial and in a control group of patients receiving carboplatin alone. Total Pt, ultrafilterable Pt, and intact carboplatin concentrations were determined in plasma, and the major carboplatin-DNA adducts G-Pt-G and Pt-GG (10) were determined in WBCs.

MATERIALS AND METHODS

Patients. This pharmacokinetic study was performed within the context of a Phase I trial, using escalating doses of carboplatin with amifostine protection, which was performed both in our hospital and in the University Hospital in Nijmegen (11). In this study, amifostine was given just before and at 2 and 4 h after the start of the carboplatin infusion in a 4-weekly interval regimen. This treatment schedule was thought to give a better protection against carboplatin-induced toxicities than a single administration of amifostine, because the half-life of WR 1065, the active metabolite of amifostine (t½, 0.19 h; Ref. 12), is short in comparison to the half-life of carboplatin.

The abbreviations used are: Pt, platinum; Clcr, creatinine clearance; AUC, area under the concentration-time curve.
Thirty-four patients were entered in this study and were either treated with carboplatin alone or with carboplatin in combination with three doses of amifostine. Five of them received both treatment schedules, i.e., carboplatin as a single agent during the first cycle and carboplatin in combination with amifostine in the second cycle, four weeks later. This intra-patient comparison was only possible in patients treated at the starting dose level of carboplatin, i.e., 400 mg/m². In total, 40 cycles were studied: 27 cycles of carboplatin and amifostine and 13 cycles of carboplatin alone. We were unable to investigate the complete pharmacokinetic profile (plasma pharmacokinetics, Pt-DNA adducts in WBCs, and the cumulative urinary excretion) during every cycle. In some patients, only the Pt-DNA adduct levels or the cumulative urinary excretion was measured.

Patients were classified according to their creatinine clearance, which was calculated from the serum creatinine level with the Cockcroft formula (13). Twenty-one patients had a creatinine clearance of above 80 ml/min, and 11 patients had a creatinine clearance between 50 and 80 ml/min. One patient had a severely impaired kidney function (Clcr, 33 ml/min). Contrary to the other patients, this patient received a reduced dose of carboplatin (135 mg/m²).

Drug Administration. Carboplatin (150 mg of lyophilized carboplatin/vial with 150 mg of mannitol; Bristol Myers Squibb, Woerden, the Netherlands) was reconstituted and diluted to a total volume of 165 ml with 5% dextrose. Amifostine (500 mg lyophilized amifostine/vial with 500 mg of mannitol; USB Pharma, Nijmegen, the Netherlands) was reconstituted and diluted to a total volume of 55 ml with 0.9% NaCl. Both drugs were administered as 15-min i.v. infusions by using syringe infusion pumps. Amifostine was administered three times, i.e., immediately before carboplatin and at 2 and 4 h after the start of the carboplatin infusion. Carboplatin was administered at a dose of 400 or 500 mg/m², except for the patient with the severely impaired kidney function, who received 135 mg/m². In some patients who participated in the Phase I study, the dose of carboplatin went up to 720 mg/m². Amifostine was initially administered at a dose of 910 mg/m² (n = 2). However, non-hematological toxicity forced us to reduce the dose of amifostine to 740 mg/m² (n = 23; Ref. 11).

All patients received at least 1 liter of normal saline before treatment to reduce the chance of hypotension during the amifostine administration. Blood pressure was recorded every 5 min during each amifostine administration to allow an interruption of the infusion when severe hypotension occurred.

Sampling. For plasma pharmacokinetics, blood samples of 6 ml were taken in cooled heparinized tubes just before treatment, at the end of the carboplatin infusion, and at 30 min and 1, 2, 4, 8, 11, 22, and 24 h after the start of the carboplatin administration. At 4, 8, 11, and 22 h after the start, 18 ml of blood were collected for the additional analysis of Pt-DNA adducts in the leukocytes. Urine was collected during the first 24 h after starting the carboplatin treatment.

Sample Pretreatment. Blood samples were immediately placed on ice and centrifuged at 2000 × g for 5 min at 4°C. Plasma was ultrafiltered (1500 × g for 30 min at 15°C) using MPS-1 systems provided with YMT filters (Amicon, Capelle a/d Ijssel, the Netherlands). The plasma ultrafiltrate was chromatographed in duplicate (2 × 100 µl) on a reversed phase column [microspher C18 3µ, 100 × 4.6-mm; mobile phase, 1 mM phosphate buffer (pH = 7.0)], and the fractions containing intact carboplatin were collected. The RBCs were washed once with PBS. Plasma, plasma ultrafiltrate, carboplatin fractions, and RBCs were stored at −20°C until Pt analysis. For the analysis of Pt-DNA adducts, 27 ml of whole blood was stored at −80°C until analysis. The urine fractions were pooled and after measuring of the total volume, an aliquot was stored at −20°C for Pt determination.

Analytical Methods. Plasma samples were diluted 10 or 30 times with 0.38 M NaCl in 0.5 M HCl and 0.1% Triton X/Antifoam B. Plasma ultrafiltrate samples were diluted 2.5 or 25 times with 0.15 M NaCl in 0.2 M HCl. The intact carboplatin-containing column fractions were evaporated and reconstituted in water. The urine samples were diluted 10 times with 0.15 M NaCl in 0.2 M HCl. RBCs were destroyed overnight with 0.5 ml benzethoniumhydroxide (Sigma Chemical Co., Zwijndrecht, the Netherlands; at 55°C) and diluted with 4.25 ml 0.2 M hydrochloric acid. Calibration standards and quality control samples were prepared by spiking blank plasma, plasma ultrafiltrate, urine, and RBCs and were treated the same way as the patient samples. The Pt concentrations were measured with flameless atomic absorption spectrophotometry (Spectra AA-300 Zeeman AAS; Varian, Houten, the Netherlands).

For the analysis of the carboplatin-DNA adducts, the DNA was isolated from the leukocytes followed by immunochromchemical detection of the Pt-DNA adducts (ELISA; Refs. 14 and 15).

Pharmacokinetic Analysis. The pharmacokinetic parameters were calculated by the pharmacokinetic data analysis program Topfit 2.0 (Gustav Fischer, Stuttgart, Germany). For total Pt and ultrafilterable Pt, a three-compartmental analysis resulted in the best curve fit, whereas for intact carboplatin, a two-compartment model was most suitable. This was established by inspection and Akaike Information Criterion. A weight factor of 1/y was applied. The results of the two- or three-compartmental analysis, especially the AUC value (calculated by using the macro rate constants) and the final half-life, were compared with the results obtained with the noncompartmental data analysis to check the quality of the compartmental curve fit. For the calculation of the final half-life in the noncompartmental data analysis, the three final data points were used, i.e., for total Pt and ultrafilterable Pt, t = 11, 22, and 24 h, and for intact carboplatin, t = 4, 8, and 11 h. For approximately six plasma concentration-time curves, the three-compartmental curve fitting of total or ultrafilterable Pt resulted in an unrealistic long final half-life, when compared to the results from the noncompartmental analysis. In that case, the curve was fitted again with the three-compartmental analysis after fixation of the elimination rate constant to the value obtained from the noncompartmental analysis. Because there were no indications to assume that the carboplatin pharmacokinetics were not linear with increasing doses, the AUC values were normalized to 400 mg/m² to compare the pharmacokinetic data of patients treated at different dose levels of carboplatin.

The pharmacokinetics of carboplatin was investigated during 12 courses after treatment with carboplatin alone and during 16 courses of patients treated with carboplatin in combination with amifostine. The pharmacokinetic data of one of the patients...
who was treated with carboplatin alone and 4 weeks later with carboplatin and amifostine could not be integrated in the results of the two treatment groups, because of the severely impaired kidney function of the patient (Clcr, 33 ml/min). The data of this patient were only used for a within-patient comparison.

Statistics. Student's t test was used for the statistical evaluation of the results.

RESULTS

The pharmacokinetic analyses were based on three different Pt species: total Pt, ultrafilterable (not protein-bound) Pt, and intact carboplatin. In Fig. 1, the plasma concentration-time curves of these three components are shown for a patient, who was first treated with carboplatin alone and 4 weeks later with carboplatin and amifostine. An increase in the ultrafilterable Pt and intact carboplatin concentrations was observed after treatment with carboplatin in combination with amifostine. This was observed only in the final part of the plasma concentration-time curves, suggesting a change in the final half-lives. The means of the pharmacokinetic parameters of the total group of patients after treatment with carboplatin with and without amifostine are shown in Tables 1 and 2. Because carboplatin is predominantly excreted via the kidneys, the pharmacokinetic parameters are highly dependent on the renal function of a patient. Therefore, the results of the patients were split up according to their creatinine clearance. Table 1 shows the results in patients with a normal kidney function (Clcr > 80 ml/min), whereas in Table 2, the results are summarized in patients with an impaired kidney function (50 < Clcr < 80 ml/min). The AUC values were normalized to a dose of 400 mg/m². The individual data of the AUC values and the final half-lives are shown in Figs. 2 and 3.

The pharmacokinetic parameters after treatment with carboplatin alone were comparable to results reported previously (16). When comparing these data with those after treatment with carboplatin in combination with amifostine, no influence of amifostine on the AUC value of total Pt was observed both in patients with a normal renal function and in patients with an impaired kidney function (Tables 1 and 2, Fig. 2). However, the AUC values of ultrafilterable Pt and intact carboplatin, which are thought to be more related to cytotoxicity than total Pt, seemed to increase under the influence of the amifostine treatment. This increase was more pronounced in patients with an impaired renal function (P < 0.05 for ultrafilterable Pt). The AUC value for total Pt in the erythrocytes of the patients with a normal renal function was not influenced by amifostine. In the patients with an impaired kidney function, an increase in AUC value was observed, but this included only a small number of patients (Tables 1 and 2). The half-lives of the triphasic decrease of total Pt in plasma were not influenced by amifostine, although in both groups (with normal and impaired kidney function) there was a trend for a decreased final half-life after administration of amifostine (Tables 1 and 2; Fig. 3). For ultrafilterable Pt, an increase of f\textsubscript{1/2a} and f\textsubscript{1/2γ} was observed, but this was only significant for f\textsubscript{1/2γ}. In the case of intact carboplatin, a significant increase in final half-life (f\textsubscript{1/2b}) was observed only in the patients with an impaired kidney function. The mean residence time showed a tendency to decrease for total Pt and to increase for ultrafilterable Pt and intact carboplatin after treatment with amifostine. This was only significant in the case of ultrafilterable Pt in patients with a normal renal function. The total body clearance and the distribution volume were not significantly influenced by amifostine. No difference in the cumulative urinary excretion was observed between patients treated with carboplatin alone and patients treated with carboplatin and amifostine (Tables 1 and 2).

In the patient with the severely impaired kidney function (Clcr = 33 ml/min), the same trends were observed when comparing the pharmacokinetic parameters after treatment with carboplatin alone during the first course with those after treat-
### Table 1 Pharmacokinetic parameters (mean ± SD) of total platinum (TPt), ultrafilterable platinum (UFPt), and intact carboplatin after treatment with carboplatin alone (CA) or in combination with amifostine (CAWR) in patients with a normal renal function (Clcr > 80 ml/min)

<table>
<thead>
<tr>
<th>Pt species</th>
<th>Treatment</th>
<th>n</th>
<th>AUCa (μM·h)</th>
<th>t1/2a (h)</th>
<th>t1/2b (h)</th>
<th>t1/2γ (h)</th>
<th>MRT (h)</th>
<th>CI (ml/min/1.73 m²)</th>
<th>Vss (liter 1.73 m²)</th>
<th>n</th>
<th>AUC (nmol/g/min)</th>
<th>n</th>
<th>Ae (% of dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPt</td>
<td>CA</td>
<td>8</td>
<td>447 ± 61</td>
<td>0.10 ± 0.07</td>
<td>1.45 ± 0.27</td>
<td>26.7 ± 11.4</td>
<td>20.5 ± 7.1</td>
<td>69.4 ± 11.0</td>
<td>89.6 ± 37.5</td>
<td>4</td>
<td>2999 ± 523</td>
<td>7</td>
<td>68.0 ± 12.1</td>
</tr>
<tr>
<td></td>
<td>CAWR</td>
<td>12</td>
<td>445 ± 70</td>
<td>0.13 ± 0.08</td>
<td>1.48 ± 0.20</td>
<td>19.6 ± 5.5</td>
<td>17.9 ± 7.0</td>
<td>69.8 ± 10.7</td>
<td>68.5 ± 17.8</td>
<td>11</td>
<td>3020 ± 789</td>
<td>12</td>
<td>72.3 ± 8.2</td>
</tr>
<tr>
<td>UFPt</td>
<td>CA</td>
<td>7</td>
<td>264 ± 43</td>
<td>0.15 ± 0.08</td>
<td>1.23 ± 0.28</td>
<td>3.5 ± 0.5</td>
<td>2.48 ± 0.33</td>
<td>117.5 ± 16.8</td>
<td>17.1 ± 2.8</td>
<td>4</td>
<td>2999 ± 523</td>
<td>7</td>
<td>68.0 ± 12.1</td>
</tr>
<tr>
<td></td>
<td>CAWR</td>
<td>12</td>
<td>286 ± 57</td>
<td>0.10 ± 0.04</td>
<td>1.42 ± 0.26</td>
<td>5.0 ± 1.2b</td>
<td>3.24 ± 0.61b</td>
<td>109.5 ± 19.5</td>
<td>20.4 ± 4.0</td>
<td>11</td>
<td>3020 ± 789</td>
<td>12</td>
<td>72.3 ± 8.2</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>CA</td>
<td>8</td>
<td>245 ± 33</td>
<td>0.32 ± 0.23</td>
<td>2.0 ± 0.3</td>
<td>2.12 ± 0.31</td>
<td>126.0 ± 14.8</td>
<td>16.2 ± 2.8</td>
<td>4</td>
<td>2999 ± 523</td>
<td>7</td>
<td>68.0 ± 12.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CAWR</td>
<td>11</td>
<td>256 ± 48</td>
<td>0.18 ± 0.07</td>
<td>2.1 ± 0.4</td>
<td>2.28 ± 0.38</td>
<td>119.6 ± 21.7</td>
<td>16.2 ± 4.2</td>
<td>11</td>
<td>3020 ± 789</td>
<td>12</td>
<td>72.3 ± 8.2</td>
<td></td>
</tr>
</tbody>
</table>

a AUC, area under the plasma concentration-time curve normalized to a dose of 400 mg/m²; t1/2a, distribution half-life; t1/2b, initial elimination half-life; t1/2γ, terminal elimination half-life; MRT, mean residence time; CI, total body clearance; Vss, apparent volume of distribution at steady state; Ae, cumulative urinary excretion over the first 24 h.
b P < 0.01.

### Table 2 Pharmacokinetic parameters (mean ± SD) of total platinum (TPt), ultrafilterable platinum (UF Pt), and intact carboplatin after treatment with carboplatin alone (CA) or in combination with amifostine (CAWR) in patients with an impaired renal function (50 < Clcr < 80 ml/min)

<table>
<thead>
<tr>
<th>Pt species</th>
<th>Treatment</th>
<th>n</th>
<th>AUCa (μM·h)</th>
<th>t1/2a (h)</th>
<th>t1/2b (h)</th>
<th>t1/2γ (h)</th>
<th>MRT (h)</th>
<th>CI (ml/min/1.73 m²)</th>
<th>Vss (liter 1.73 m²)</th>
<th>n</th>
<th>AUC (nmol/g/min)</th>
<th>n</th>
<th>Ae (% of dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPt</td>
<td>CA</td>
<td>4</td>
<td>594 ± 139</td>
<td>0.06 ± 0.04</td>
<td>1.56 ± 0.20</td>
<td>22.5 ± 5.0</td>
<td>23.2 ± 10.6</td>
<td>50.0 ± 17.9</td>
<td>59.4 ± 13.4</td>
<td>4</td>
<td>2942 ± 523</td>
<td>3</td>
<td>58.2 ± 25.0</td>
</tr>
<tr>
<td></td>
<td>CAWR</td>
<td>4</td>
<td>620 ± 89</td>
<td>0.11 ± 0.04</td>
<td>1.78 ± 0.30</td>
<td>16.0 ± 2.1</td>
<td>15.6 ± 1.0</td>
<td>52.5 ± 7.8</td>
<td>47.1 ± 6.3</td>
<td>3</td>
<td>3827 ± 359b</td>
<td>4</td>
<td>64.5 ± 17.3</td>
</tr>
<tr>
<td>UFPt</td>
<td>CA</td>
<td>4</td>
<td>280 ± 62</td>
<td>0.08 ± 0.07</td>
<td>1.41 ± 0.40</td>
<td>4.2 ± 0.2</td>
<td>3.29 ± 0.39</td>
<td>102.3 ± 22.5</td>
<td>19.3 ± 4.1</td>
<td>4</td>
<td>2942 ± 523</td>
<td>3</td>
<td>58.2 ± 25.0</td>
</tr>
<tr>
<td></td>
<td>CAWR</td>
<td>4</td>
<td>395 ± 59b</td>
<td>0.19 ± 0.07</td>
<td>1.70 ± 0.40</td>
<td>5.6 ± 0.8b</td>
<td>4.97 ± 1.58</td>
<td>82.8 ± 13.7</td>
<td>22.9 ± 2.8</td>
<td>3</td>
<td>3827 ± 359b</td>
<td>4</td>
<td>64.5 ± 17.3</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>CA</td>
<td>4</td>
<td>247 ± 69</td>
<td>0.22 ± 0.04</td>
<td>2.2 ± 0.2</td>
<td>2.49 ± 0.39</td>
<td>118.2 ± 31.3</td>
<td>17.2 ± 4.5</td>
<td>3</td>
<td>3155 ± 575</td>
<td>9</td>
<td>53.8 ± 25.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CAWR</td>
<td>4</td>
<td>349 ± 49</td>
<td>0.29 ± 0.11</td>
<td>2.8 ± 0.4b</td>
<td>3.15 ± 0.57</td>
<td>93.5 ± 16.1</td>
<td>17.5 ± 1.7</td>
<td>3</td>
<td>3155 ± 575</td>
<td>9</td>
<td>53.8 ± 25.0</td>
<td></td>
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</table>

a AUC, area under the plasma concentration-time curve normalized to a dose of 400 mg/m²; t1/2a, distribution half-life; t1/2b, initial elimination half-life; t1/2γ, terminal elimination half-life; MRT, mean residence time; CI, total body clearance; Vss, apparent volume of distribution at steady state; Ae, cumulative urinary excretion over the first 24 h.
b P < 0.05.
ment with carboplatin and amifostine during the second course. After treatment with amifostine, the AUC values in this patient increased, from 121 to 1465, from 778 to 847, and from 640 to 687 μM·h for total Pt, ultrafilterable Pt, and intact carboplatin, respectively. These data related to increases in final half-lives from 15.4 to 17.3, 5.5 to 7.7, and 3.6 to 4.8 h for total Pt, ultrafilterable Pt, and intact carboplatin, respectively.

When comparing the results of Table 1 with those in Table 2, the influence of the creatinine clearance on the pharmacokinetics of carboplatin is clear. In general, final half-lives and AUC values were increased, whereas total body clearance and cumulative urinary excretion decreased in patients with an impaired kidney function. Surprisingly, the final half-life of total Pt decreased in patients with a lower Clcr.

The increase in final half-life of ultrafilterable Pt by amifostine suggested an influence of this agent on the renal clearance of carboplatin, which was, however, not confirmed by a decrease in the cumulative urinary excretion. However, we investigated whether the addition of amifostine to carboplatin had an impact on the serum creatinine levels. Indeed, the serum creatinine concentration (mean ± SD) significantly changed (P < 0.0001) between 24 and 0 h after the start of treatment with carboplatin in combination with amifostine (34.1 ± 17.2%, n = 15) in comparison to carboplatin alone (−1.8 ± 16.5%, n = 9).

In Table 3, the values of the major carboplatin-DNA adducts Pt-GG and G-Pt-G (mean ± SD) are given for blood samples taken at different time points after the start of the treatment. Because the adduct levels were very low (the detection limit is about 0.15 fmol/μg DNA), the variation was rather high. However, there was no indication for any influence of amifostine on the formation or repair of the carboplatin-DNA adduct levels. No correlation could be found between the DNA adduct levels and the AUC of ultrafilterable Pt (r² = 0.1–0.7).

**DISCUSSION**

Our results indicate that treatment with amifostine influences the pharmacokinetics of carboplatin in patients. The final
Effect of Amifostine on Carboplatin Pharmacokinetics

Table 3 Pt-DNA adduct levels (mean ± SD) in leukocytes of patients treated with carboplatin alone (CA) or in combination with amifostine (CAWR)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Treatment</th>
<th>n</th>
<th>Pt-GG (fmol/μg DNA)</th>
<th>G-Pt-G (fmol/μg DNA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>CA</td>
<td>2</td>
<td>0.16 ± 0.04</td>
<td>0.18 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>CAWR</td>
<td>7</td>
<td>0.22 ± 0.23</td>
<td>0.33 ± 0.50</td>
</tr>
<tr>
<td>8</td>
<td>CA</td>
<td>5</td>
<td>0.22 ± 0.15</td>
<td>0.36 ± 0.31</td>
</tr>
<tr>
<td></td>
<td>CAWR</td>
<td>15</td>
<td>0.17 ± 0.08</td>
<td>0.24 ± 0.14</td>
</tr>
<tr>
<td>11</td>
<td>CA</td>
<td>5</td>
<td>0.25 ± 0.10</td>
<td>0.32 ± 0.11</td>
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<tr>
<td></td>
<td>CAWR</td>
<td>15</td>
<td>0.20 ± 0.09</td>
<td>0.19 ± 0.10</td>
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<tr>
<td>22</td>
<td>CA</td>
<td>3</td>
<td>0.21 ± 0.10</td>
<td>0.19 ± 0.05</td>
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<td>CAWR</td>
<td>8</td>
<td>0.19 ± 0.10</td>
<td>0.16 ± 0.06</td>
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</table>

<table>
<thead>
<tr>
<th>Ccr &gt; 80 ml/min</th>
<th>50 &lt; Ccr &lt; 80 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt-GG (fmol/μg DNA)</td>
<td>G-Pt-G (fmol/μg DNA)</td>
</tr>
<tr>
<td>2</td>
<td>0.16 ± 0.15</td>
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Unpublished results.

Half-lives of ultrafilterable Pt and intact carboplatin were increased (Table 1; Fig. 3). This may be explained by an influence of amifostine on the distribution of carboplatin. However, an influence of amifostine on the renal clearance of carboplatin is a more plausible explanation because an increase in serum creatinine concentration was observed in patients treated with carboplatin in combination with amifostine. This increase was only transient and completely reversible, because within 1 week, serum creatinine levels returned to normal in all cases. As a result, the AUCs of the Pt species increased, but only to a small extent, because only the relatively low concentrations at the end of the curve were enhanced.

The influence of amifostine on the renal clearance of carboplatin, however, was not accompanied by a decrease in the cumulative urinary excretion. This suggested that the reduction of the kidney function was not an immediate effect of amifostine but mainly manifested itself after 6 h when most of the free carboplatin was already excreted in the urine (17).

For total Pt, no increase in final half-life was observed, but instead a trend for a decrease in final half-life was seen when amifostine was administered. In combination with the observed increase in the final half-life of ultrafilterable Pt, this suggests a possible change in the binding of carboplatin to proteins. However, in vitro, amifostine nor its active metabolite WR 1065 has an influence on the protein binding of carboplatin. Surprisingly, when the final half-life of total Pt in patients with an impaired renal function was compared to the final half-life in patients with a normal kidney function, a decrease instead of an increase in final half-life of total Pt was observed (Table 1 versus 2). This suggests that the final half-life of total Pt is not primarily dependent on the kidney function. As reported earlier for cisplatin, it is largely dependent on the turnover rate of the proteins to which the Pt compound binds irreversibly (18). In contrast, for Pt-DNA adducts, it is thought to be based on the prevention of the formation of Pt-DNA adducts in normal tissues, a decrease in Pt-DNA adduct levels would have been expected. However, the observed influence of amifostine on the pharmacokinetics of carboplatin resulting in higher ultrafilterable Pt concentrations in plasma would possibly result in the opposite effect. Because of the low Pt-DNA adduct levels and the large variation, no conclusion can be drawn.

Our results regarding the influence of amifostine on the AUC and final half-life of, especially, ultrafilterable Pt do not correspond to data reported previously. Budd et al. (19) reported that no pharmacokinetic interaction between carboplatin and amifostine was observed in patients treated with carboplatin in combination with two doses of amifostine. However, this was investigated in only four patients, and no control group was included in this study.

In nude mice studies, treatment with carboplatin in combination with amifostine not only resulted in an increase of Pt concentrations in plasma ultrafiltrate but also in tumor and normal tissues. This was probably the explanation for the observed increase in antitumor activity of carboplatin when combined with amifostine (9). Whether this effect also occurs in patients is still unclear. The influence of amifostine on the plasma pharmacokinetics of carboplatin was less pronounced in patients than in nude mice, and the influence on the Pt concentrations in tissues, especially tumor tissue, in patients is still unknown. In patients, the influence of amifostine on the pharmacokinetics of carboplatin was observed in the last part of the Pt concentration-time curve. Thus, the effect of amifostine was only observed on relatively low Pt concentrations. Therefore, the clinical relevance of this pharmacokinetic interaction is uncertain, and whether amifostine has an impact on the efficacy of carboplatin in patients still needs to be established. There is no reason to assume that the pharmacokinetic interaction between carboplatin and amifostine will have a negative effect on the reduction of the carboplatin-induced toxicities by amifostine. The maximum tolerated dose of carboplatin, given in combination with three doses of amifostine, was increased to 500 mg/m² in patients treated previously and 720 mg/m² in chemo-naive patients (20). Dose-limiting toxicity on both occasions consisted of myelosuppression, with two of five patients showing grade 4 neutropenia and three of five showing grade 4 thrombocytopenia at the highest dose level in the chemo-naive
patients. Additional details about the toxicities observed during the Phase I trial will be part of a separate report.

In conclusion, the treatment of patients with carboplatin in combination with three doses of amifostine resulted in an increase in the half-life of ultrafilterable Pt and a small decrease in the final half-life of ultrafilterable Pt and a small increase in the AUC value. This pharmacokinetic effect could be due to a direct influence of amifostine on kidney function, because also an increase in serum creatinine level was observed. The clinical relevance of this influence is still unclear. However, theoretically it might result in an increase in the efficacy of carboplatin, as has been observed in tumor-bearing nude mice.

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REFERENCES


Pharmacokinetics of carboplatin with and without amifostine in patients with solid tumors.

A E Korst, M L van der Sterre, C M Eeltink, et al.