Cancer Chemother Pharmacol (1990) 27: 55–59

Cancer Chemotherapy and Pharmacology

Pharmacokinetics of cisplatin given at a daily low dose as a radiosensitiser

G. Milano[1], V. Troger[2], A. Courdi[1], X. Fontana[1], P. Chauvel[1], J. L. Lagrange[1]

[1] Centre Antoine-Lacassagne, 36 voie Romaine, F-06054 Nice Cedex, France
[2] Institut Jules-Bordet, 1 rue Heger-Bordet, 1000 Bruxelles, Belgique

Summary. A total of 25 patients with inoperable cervical cancer were treated by daily radiotherapy (2 Gy); sensitisation was obtained by administration of 5 mg cisplatin 30 min before each irradiation session. The total cumulative dose of cisplatin varied between 50 and 150 mg. A complete kinetic profile (0–24 h) of platinum (Pt) was established after the first dose and at the end of treatment for 22 patients. Pt was quantified by atomic absorption spectrophotometry using Zeeman-effect background correction for trace analysis. The total Pt $AUC_{0-24\,h}$ increased from 1.53 ± 0.77 to 7 ± 3.55 $\mu g \cdot h \cdot ml^{-1}$ between the start and the end of treatment ($P < 0.001$). Ultrafilterable Pt (Pt UF) rose from 0.079 ± 0.038 to 0.138 ± 0.095 $\mu g \cdot h \cdot ml^{-1}$ ($P < 0.01$). Elimination half-lives were unchanged for total Pt but rose for Pt UF; these kinetic modifications in Pt UF did not correlate with any significant change in individual serum creatinine levels. No clear correlation was found between the cumulative cisplatin dose and tumor levels measured in 13 patients, and the tumor cisplatin dose did not correlate with response to treatment. Patients with hematological toxicity were characterised by an increase in their residual Pt UF level during treatment. Overall, our findings strengthen the notion of Pt UF kinetic variability during repeated treatment.

Introduction

The particularly interesting and apparently complex interaction between cisplatin (CDDP) and radiation has prompted numerous experimental and therapeutic trials in clinical oncology, as discussed in two reviews [2, 16]. However, the origin of this CDDP-radiation interaction is poorly understood [2, 16], and the clinical trials conducted to date were designed more on empiric bases than on rational guidelines. There is currently no general consensus on the optimal drug dose or the timing or sequencing of administration of the drug and irradiation. Since most experimental in vivo data [2, 6] suggest that CDDP is most effective when given a short time before irradiation, it seemed logical to apply this sequence in patients as well. Van Harskamp et al. [17] recently reported interesting therapeutic results obtained with a combination of daily low-dose CDDP plus radiotherapy for inoperable, non-small-cell lung cancer.

Our institute recently initiated a pilot study based on the same principle of daily, low-dose CDDP plus radiotherapy for a group of 25 patients with inoperable cervical cancer. The daily CDDP dose (5 mg) was given 30 min before irradiation (1.8–2 Gy) for 2–5 weeks, depending on the patient's disease stage. Evaluation of CDDP pharmacokinetics in this trial had two purposes: (1) to obtain better knowledge of the treatment itself by searching for pharmacokinetic-pharmacodynamic associations using analysis of blood levels as well as tumor drug concentrations; and (2) to investigate the effects of long-term treatment on the variability in CDDP kinetics; such information has not yet been available despite extensive documentation of CDDP pharmacokinetics [1]. A complete kinetic profile was established for each patient at the beginning and end of the treatment period. Additional blood samples were obtained every week during treatment, and biopsies were performed in most patients for tumor assays.

Patients and methods

The study population consisted of 25 patients (mean age, 49 years; range, 29–68 years) with histologically confirmed, nonresectable cervical cancer (Table 1). All patients were treated with daily radiotherapy (1.8–2 Gy) delivered 30 min after a short infusion (5 min) of CDDP (5 mg in 50 ml 0.9% NaCl on 5 consecutive days every week. Patients with stage II disease were treated for 2 weeks (cumulative doses: 20 Gy, 50 mg CDDP); patients with stage III/IV disease underwent 6 weeks of therapy (cumulative doses: 60 Gy, 150 mg CDDP). Before the start of treatment, all patients had normal renal function (blood creatinine value, <150 μmol/l), a Karnofsky performance status of at least 60% and a life expectancy of at least 12 weeks. Renal function (blood electrolytes, urea

Offprint requests to: G. Milano

Table 1. Study population and major pharmacokinetic parameters

Patient (age in years)	Protocol[a]	Previous therapy	Response to treatment	Treatment toxicity ≥ grade 3	Plasma creatinine (μmol/l)		Total Pt AUC (μg·h·ml^{-1})		Pt UF AUC (μg·h·ml^{-1})		Tumor μg/g (cumulative dose of CDDP, mg)
					Before treatment	After treatment	S	E	S	E	
1 (55)	B	No	CR	Yes, H	71	79	1.66	11.45	0.085	0.095	0.13 (50)
2 (56)	B	No	PR	No	62	62	1.65	9.96	0.100	0.200	0.25 (125)
3 (29)	A	No	PR	No	89	79	0.99	5.77	0.048	0.112	0.30 (75)
4 (46)	B	No	NR	Yes, H	150	145	2.76	4.63	0.198	0.350	0.30 (50)
5 (59)	B	No	PR	No	62	62	1.13	5.20	0.093	0.076	0.48 (50)
6 (38)	A	No	CR	Yes, H	71	71	0.30	4.91	0.057	0.070	
7 (58)	B	No	CR	Yes, H	71	79	1.91	6.54	0.042	0.111	0.54 (100)
8 (49)	B	No	NR	No	53	62	1.85	9.59	0.064	0.136	
9 (37)	A	No	NE	No	62	62	1.23	5.08	0.140	0.013	
10 (42)	B	No	PR	No	79	79	0.160	1.39	0.022	0.062	
11 (46)	B	No	NE	No	79	88	0.22	1.23	0.053	0.110	
12 (56)	B	Yes CI	PR	No	140	150	2.74	8.10	0.087	0.040	
13 (45)	A	No	PR	No	71	71	1.37	6.15	0.108	0.050	0.04 (50)
14 (50)	B	No	CR	No	115	132	–	–	–	–	0.59 (50)
15 (55)	B	No	PR	No	88	88	2.40	13.70	0.098	0.250	0.30 (75)
16 (56)	B	No	PR	No	79	89	–	–	–	–	1.10 (50)
17 (49)	A	Yes RI	PR	No	63	63	2.34	6.96	0.093	0.062	0.09 (50)
18 (47)	B	Yes	NE	Yes, H	97	106	2.74	4.20	0.073	0.330	
19 (55)	B	No	NR	No	81	81	1.09	5.40	0.066	0.260	0.22 (125)
20 (35)	B	No	NR	No	72	63	1.45	12.70	0.077	0.126	
21 (49)	B	No	NR	No	106	90	–	–	–	–	0.26 (125)
22 (45)	A	No	NR	No	54	54	1.30	4.58	0.048	0.240	
23 (45)	A	No	PR	No	54	54	1.13	4.79	0.068	0.036	
24 (68)	B	No	NE	No	72	72	1.38	13.70	0.095	1.150	
25 (56)	A	No	NR	No	72	72	1.78	8.06	0.043	0.166	
49		←Mean→			76.5	82.12	1.53	7.00	0.079	0.138	0.35
8.7		←Standard deviation→			26.9	26	0.77	3.55	0.038	0.095	0.27
Statistics					NS		P <0.001		P <0.01		

[a] A = 2 weeks' treatment; B = 6 weeks' treatment (for details see Patients and methods)

CT, chemotherapy; RT, radiotherapy; NE, not evaluable; H, hematological toxicity; Pt UF, ultrafilterable platinum in plasma; S, start of treatment; E, end of treatment; tumor, intratumoral concentrations

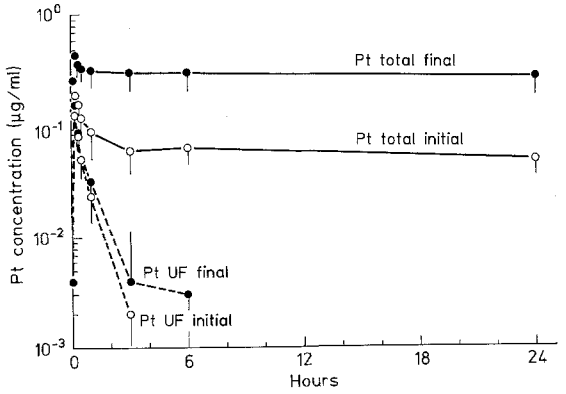

Fig. 1. Blood disposition of total (*Pt total*) and ultrafilterable platinum (*Pt UF*) after the first and last injections of CDDP. *Vertical bars* represent standard deviations

and creatinine) and hematological function (RBC, WBC, platelet count) were evaluated every week during treatment. Toxicity was graded using WHO recommendations. Response to treatment was evaluated at the end of the treatment period; a complete response (CR) corresponded to the disappearance of all clinically visible or palpable lesions, a partial response (PR) was defined as tumour regression of >50%; no response (NR) corresponded to tumour regression of ≤50%, stable disease or progressive disease.

Pharmacokinetic study. All pharmacokinetic parameters were analysed for 22 patients after the first and last CDDP doses. Blood samples were obtained immediately before injection and at 10, 20, 30 and 60 min and 3, 6 and 24 h after injection. Residual blood levels of cisplatin were measured every week, just before the daily injection, in 17 patients. Tumor biopsies were performed in 13 patients at various times (between 2 and 5 weeks) during treatment to assess tumor platinum (Pt) levels.

Treatment of samples

Blood. Blood samples (3 ml) obtained in ethylenediaminetetraacetic acid (EDTA) tubes were immediately placed in a water bath containing ice for transportation to the laboratory (within 10–15 min), then centrifuged at 4° C. A 500 µl aliquot of the resulting plasma was centrifuged for 30 min at 2,000 *g* and 4° C in a Centrifree micropartition unit (Amicon, Denvers, Mass., USA). The resulting ultrafiltrate fractions were used to measure filterable Pt. Total Pt was measured in the whole plasma fraction. Samples were stored at –20° C until analysis.

Biopsies. Biopsies (1–2 mg) were taken from the accessible tumor mass; excess blood was removed, and the tissue sample was placed in a screw-top plastic tube that was stored at –20° C until analysis. Biopsies were then weighed (wet weight) and digested overnight by 500 µl 50% nitric acid, then homogenised in a glass-glass potter. The homogenate was dried under a nitrogen stream (50° C), and the dried residue was dissolved in 200 µl H_2O.

Pt assay. Quantitative analysis of Pt in samples was performed by atomic absorption spectrophotometry (AAS) using a Perkin-Elmer model 3030 atomic absorption spectrophotometer with background correction by the Zeeman effect for trace analysis. Ultrafiltrates and biopsy extracts were measured without dilution; before analysis plasma was diluted to 1/2 using a 0.2% HNO_3 solution containing 0.01% Triton X-100. The injected volume was 20 µl. A standard curve (0.162, 0.325 and 0.65 µg Pt/ml) was automatically plotted by an auto-sampler using a spiked blank plasma specimen that had previously been diluted to 1/2 (0.65 µg Pt/ml). Analysis included the following steps: drying at 110° C for 40 s; ashing at 1,400° C for 20 s and atomisation at 2,650° C with a 3-s stop flow; and tube cleaning at 2,650° C for 4 s. The limit of sensitivity (2 times the noise) was 5 ng/ml for plasma and 2.5 ng/ml for ultrafiltrates and biopsies. Reproducibility was calculated from 25 successive series of analyses; it was 8.5%, 7.6% and 6.5% for Pt concentrations of 0.162, 0.325 and 0.65 µg/ml, respectively.

Table 2. Residual plasma levels of ultrafilterable Pt

Patient number	Number of weeks after start of treatment					
	1	2	3	4	5	6
1[a]	ND	ND	10	10	15	25
3	5	ND	ND	–	–	–
4[a]	5	5	ND	ND	15	–
5	ND	ND	ND	5	ND	–
7[a]	ND	ND	3	ND	ND	3
9	ND	ND	–	–	–	–
10	ND	ND	6	3	3	–
11	ND	ND	ND	6	6	3
15	ND	8	ND	ND	8	–
16	ND	25	15	11	–	–
17	ND	ND	ND	–	–	–
18[a]	ND	3	10	3	–	–
19	ND	ND	3	3	5	–
20	ND	ND	5	ND	–	–
21	7	7	6	7	–	–
23	ND	5	–	–	–	–
24	ND	6	5	8	6	–

Values are expressed as ng/ml; ND, nondetectable (<2.5 ng/ml)
[a] Toxic cycles as indicated in Table 1

Data analysis. Pharmacocokinetic parameters (area under curves, AUC, by the trapezoidal rule; elimination half-lives, $t_{1/2}$) were computed using pharmacokinetic software based on the classic least-squares procedure (Siphar-base, Simed, Creteil, France).

Statistical evaluations. Student's *t*-test for paired samples was used to compare the pharmacokinetic parameters at the start and end of the treatment. The chi-square test was used for comparison of frequencies. The Mann-Whitney non-parametric test was used for comparison of distributions.

Results

The plasma $AUC_{0-24\,h}$ for both total Pt and ultrafilterable Pt (Table 1, Fig. 1) rose significantly between the start and the end of the treatment period. The mean increase for total body exposure to free Pt was close to 100%. There was no significant relationship between Δ = ultrafilterable Pt (end) – ultrafilterable Pt (start) and the cumulative dose of CDDP. The mean elimination half-lives of total Pt were unchanged (70 h); in the α-phase, free Pt half-lives were 0.35 h at the beginning and 0.39 h at the end of treatment (non-significant). A β-phase was identified for free Pt at the end of treatment ($t_{1/2\beta}$ = 5 h; Fig. 1). No evidence of tumor drug accumulation was seen between 2 and 5 weeks of treatment (50–125 mg cumulative CDDP; Table 1). The tumor drug level was not linked to treatment response (comparison of the drug distribution in CR + PR vs NR was non-significant).

Five patients developed hematological toxicity during treatment (≥grade 3). No renal toxicity was observed. There were no significant differences between the toxic and non-toxic cycles for the AUC of ultrafilterable Pt at the

start or end of the treatment. However, the subject with the highest pretreatment blood creatinine level (patient 4) also had the highest free Pt AUC at the start and end of the treatment. Serial residual Pt levels were available for 17 patients. Subjects who experienced hematological toxicity exhibited elevated residual blood levels of ultrafilterable Pt (threshold, 10 ng/ml) more often than did those who remained free of toxicity: 3 of 4 patients who experienced toxicity had such elevated residual drug levels vs only 1 of 13 subjects who were free of toxicity ($P < 0.01$) (Table 2).

Discussion

To date, few reports have dealt with the time-dependent characteristics of CDDP pharmacokinetics. Reece and co-workers [15] investigated 24-h ultrafilterable Pt plasma levels after the first and fourth courses of 80 mg/m^2 CDDP (2-h infusion); the AUC of ultrafilterable Pt was higher in all patients after the fourth infusion (median increase, 74%). A more recent study by Dominici et al. [7] examined CDDP pharmacokinetics in 14 patients aged 10 months through 13 years; these authors used high-dose, continuous 5-day infusions of CDDP (40 mg/m^2 daily). Courses were repeated every 28 days. The AUC of free plasma Pt increased progressively between the first and the third courses; the mean fraction of the CDDP dose excreted in urine over a 12-day period was 44% for the first course, 36% for the second and 28% for the third. These authors concluded that the progressive enhancement of body exposure to the free cytotoxic drug was attributable to reduced renal clearance. The deleterious effects of repeated and prolonged CDDP treatment on renal function have been thoroughly investigated [5, 9, 12].

In the present study, patients were treated with daily, low-dose CDDP plus synchronous radiotherapy for 5 days every week. The total cumulative CDDP dose varied with the initial disease stage (between 50 and 150 mg). Comparison of creatinine values at the start and end of treatment failed to reveal any changes in renal function (Table 1). The use of highly sensitive atomic absorption spectrometry with background correction by the Zeeman effect enabled the analysis of individual ultrafilterable Pt kinetics. Comparison of individual AUC values for ultrafilterable Pt revealed a significant rise in this parameter between the start and the end of treatment (mean increase, close to 100%). Individual differences in AUC values were not linked to the total cumulative CDDP dose. Our findings confirm and extend previous reports concerning the variability of CDDP kinetics during prolonged treatment, even at such low daily doses. In our study, modifications in total-body CDDP exposure were not related to any clear alteration in renal function as reflected by plasma creatinine values. This observation concurs with the data of Reece and co-workers [15], who demonstrated that reduced Pt elimination and an increased AUC after repeated courses of CDDP could not be predicted by changes in creatinine clearance. This apparent discrepancy can probably be explained by the fact that creatinine clearance is not a faithful indicator of renal CDDP clearance [16]; deleterious effects of prolonged exposure to CDDP on renal function may occur in other renal excretory mechanisms not reflected by creatinine homeostasis.

The only severe toxicities encountered in this study were of hematological origin. Toxic patients had higher residual ultrafilterable Pt values than did subjects who experienced no side effects (Table 2), but interpretation of this observation must take the following into account: (1) the number of cases was relatively low, (2) synchronous radiotherapy may also play a non-negligible role in this toxicity and (3) one of the toxic patients had also received pretreatment chemotherapy. Considering these limitations, our data complete the rare correlations reported to date between the pharmacokinetics and the pharmacodynamics of Pt species [4, 8, 14]. One practical application of our findings would involve weekly monitoring of residual Pt levels so as to detect patients at risk of toxicity; dose reduction or intercalation of a recovery window could then be instituted for such subjects. Daily, low-dose exposure to CDDP, which in certain cases is accompanied by the presence of detectable residual ultrafilterable Pt levels, compares favorably with continous infusion of the drug. Forastière et al. [10] recently compared the pharmacokinetics and toxicity of 5-day continuous infusion vs intermittent bolus CDDP; these authors reported that myelosuppression occurred more frequently in patients treated by continuous infusion. Total exposure to free Pt may thus contribute more to hematological toxicity than the peak levels achieved.

With the exception of animal studies [3, 13, 18], only very limited data is available on Pt concentrations in human tumors. Hecquet and colleagues [11] recently investigated tumor Pt levels in patients with advanced uterine cervical lesions who were treated with a single CDDP dose of 100 mg/m^2; 24 h later, tumor drug levels ranged between 1 and 5.9 μg/g tissue. In the present study we measured tumoral CDDP concentrations in 13 patients at different times during treatment (corresponding to cumulative CDDP doses of 50–125 mg); the lowest value obtained was 0.04 μg/g tissue and the highest, 1.1 μg/g tissue (Table 1). Taking into account the differences in the respective CDDP doses given, the concentrations we found are lower than those reported by Hecquet et al. [11]. However, we do not feel that these observations enable any conclusions to be drawn about differences between tumor Pt concentrations obtained using bolus vs continuous administration. Nevertheless, our data strongly suggest the utility of tumor Pt assays in controlled clinical trials comparing short and prolonged CDDP administration for treatment of sensitive disease localisations for which biopsies are feasible, such as cervical cancer. The tumor Pt concentrations obtained in the present study were very similar to those measured in grafted tumors of nude mice receiving an active dose of CDDP [3]. Thus, although no clear correlation was found between tumor Pt levels and treatment response in the present study, CDDP may have had specific antitumor activity as well as a radiosensitising effect.

References

1. Balis FM, Holcenberg JS, Bleyer WA (1983) Clinical pharmacokinetics of commonly used anticancer drugs. Clin Pharmacokinet 8: 202–232
2. Bellamy AS, Hill BT (1984) Interactions between clinically effective antitumor drugs and radiation in experimental systems. Biochem Biophys Acta 738: 125–166
3. Boven E, Van der Vijgh WJF, Nauta NM, Schluper HMM, Pinedo HM (1985) Comparative activity and distribution studies of five platinum analogues in nude mice bearing human ovarian carcinoma xenografts. Cancer Res 45: 86–90
4. Campbell BA, Kalman SM, Jacobs C (1983) Plasma platinum levels: relationship to cisplatin dose and nephrotoxicity. Cancer Treat Rep 67: 169–172
5. Daugaard G, Abildgaard U, Holstaine-Rathlou NH, Bruunshuus I, Bucher D, Leyssac PP (1988) Renal tubular function in patients treated with high-dose cisplatin. Clin Pharmacol Ther 44: 164–172
6. Dewitt L (1987) Combined treatment of radiation and *cis*-diamminedichloroplatinum(II): a review of experimental and clinical data. Int J Radiat Oncol Biol Phys 13: 403–426
7. Dominici C, Petrucci F, Caroli S, Alimonti A, Clerico A, Castello MA (1989) A pharmacokinetic study of high-dose continuous infusion cisplatin in children with solid tumors. J Clin Oncol 7: 100–107
8. Egorin MJ, Van Echo DA, Tipping SJ, Olman EA, Whitacre MY, Thompson BW, Aisner J (1984) Pharmacokinetics and dosage reduction of *cis*-diammine (1,1-cyclobutanedicarboxytals) platinum in patients with impaired renal function. Cancer Res 44: 5432–5436
9. Fjeldborg P, Sorensen J, Helkjaer PE (1986) The long-term effect of cisplatin on renal function. Cancer 58: 2214–2217
10. Forastière AA, Belliveau JF, Goren MP, Vogel WC, Posner MR, O'Leary GP (1988) Pharmacokinetic and toxicity evaluation of five-day continuous infusion versus intermittent bolus *cis*-diamminedichloroplatinum(II) in head and neck cancer patients. Cancer Res 48: 3869–3874
11. Hecquet B, Vennin P, Fournier C, Poissonnier B (1987) Evaluation of the pharmacological benefit and determination of the influencing factors of intra-arterial *cis*-diamminedichloroplatinum administration in patients with uterine cervical cancer. Cancer Res 47: 6134–6137
12. Jaffe N, Keifer R, Robertson R, Cangir A, Wang A (1987) Renal toxicity with cumulative doses of *cis*-diamminedichloroplatinum(II) in pediatric patients with osteosarcoma. Effect on creatinine clearance and methotrexate excretion. Cancer 59: 1577–1581
13. Litterst CL, Leroy AF, Guarino AM (1979) Disposition and distribution of platinum following parenteral administration of *cis*-dichlorodiammineplatinum(II) to animals. Cancer Treat Rep 63: 1485–1492
14. Newell DR, Siddik ZH, Gumbrell LA, Boxall FE, Gore ME, Smith IE, Calvert AH (1987) Plasma free platinum pharmacokinetics in patients treated with high dose carboplatin. Eur J Cancer Clin Oncol 23: 1399–1405
15. Reece PA, Stafford I, Russel J, Gill PG (1986) Reduced ability to clear ultrafilterable platinum with repeated courses of cisplatin. J Clin Oncol 4: 1392–1398
16. Reece PA, Stafford I, Russel J, Khan M, Gill PG (1987) Creatinine clearance as a predictor of ultrafilterable platinum disposition in cancer patients treated with cisplatin; relationship between peak ultrafilterable platinum plasma levels and nephrotoxicity. J Clin Oncol 5: 304–309
17. Van Harskamp G, Boven E, Vermorken JB, Van Deutekom H, Stam J, Njo KH, Karim ABMF, Tierie AH, Golding RP, Pinedo HM (1987) Phase II trial of combined radiotherapy and daily low-dose cisplatin for inoperable, locally advanced non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 13: 1735–1738
18. Wile AG, Kar R, Cohen RA, Jakowatz JG, Opfell RW (1986) The pharmacokinetics of cisplatin in experimental regional chemotherapy. Cancer 59: 695–700