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The influence of ageing on cisplatin pharmacokinetics in lung cancer patients with normal organ function

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Abstract This study was performed to identify any relationship between age and cisplatin (CDDP) pharmacokinetics in lung cancer patients. CDDP was given at a dose of 80 mg/m^2 by 1-h intravenous infusion to 23 lung cancer patients. All patients had normal renal, hepatic, and bone marrow functions. We measured ultrafilterable platinum (U-Pt) and total plasma platinum (T-Pt) using atomic absorption spectrometry. There was significant correlation between the age of the patients and U-Pt pharmacokinetic parameters such as the area under the plasma concentration versus time curve (AUC), total clearance (Cl), and peak plasma concentration (Cmax) as well as the AUC of T-Pt ($P < 0.05$). We performed univariate regression analysis to examine the influence of factors aside from age on the AUC of U-Pt and T-Pt. Creatinine and GPT levels were significantly related to the AUC of U-Pt, and creatinine clearance and creatinine concentrations were significantly related to the AUC of T-Pt. Therefore, stepwise multiple-regression models for the AUC of U-Pt and T-Pt were developed to assess an age effect. Age was consistently an independent and significant predictor of the AUC of U-Pt and T-Pt.

Key words: Cisplatin · Ageing · Pharmacokinetics

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Introduction

In recent years the proportion of the elderly in the Japanese population has increased, and cancer has become a very common disease in this group. Consequently, more and more elderly patients with malignancy have been treated with chemotherapy. The frequency and severity of adverse drug reactions seems higher in elderly patients [8, 9]. Despite the clear demonstration of this increased susceptibility to adverse drug reactions with age, little attention has been paid to changes in either pharmacokinetics or pharmacodynamics inherent to ageing [1, 4]. Cisplatin (CDDP) is a valuable anticancer drug with demonstrated clinical activity in the treatment of a broad spectrum of solid tumors, including lung cancer [2]. CDDP disposition varies markedly in patients receiving the drug, and multiple adverse effects are seen, including gastrointestinal toxicity and nephrotoxicity. However, knowledge of the pharmacokinetics and/or pharmacodynamics of CDDP remains limited. In this study we examined age-related differences in the pharmacokinetics of CDDP.

Patients and methods

Eligibility criteria

Patients eligible for this study had to fulfill the following criteria: histological and cytological proof of lung cancer; a performance status of 0–2 on the Eastern Cooperative Oncology Group scale [5]; a life expectancy of at least 12 weeks; recovery from all toxicities due to prior treatment and no chemotherapy within 28 days; adequate function of main organs such as the bone marrow (WBC, > 4,000/ml; platelet count, > 100,000/ml, hemoglobin level, > 9.0 g/dl), kidneys [blood urea nitrogen (BUN) concentration, < 1.5 times the upper limit of normal; creatinine level (Cre), < 1.5 times the upper limit of normal; creatinine clearance (Ccr), > 50 ml/min], and liver [bilirubin level, < 1.5 times the upper limit of normal; transaminase (GPT, GOT) value, < 2.5 times the upper limit of normal]: and no coexisting active medical problems.

Ccr was determined by the 24-h method. An indocyanine green (ICG) tolerance test was carried out prior to the start of this study. For the ICG tolerance test, blood samples were collected before and at 15 min after intravenous ICG administration at a dose of 0.5 mg/kg. The serum ICG retention rate at 15 min (ICG 15 min) was measured using a spectrophotometer. Informed consent was obtained from all patients. This study was approved by the institutional review board of the National Cancer Center Hospital.

Treatment protocol

Patients were treated with combination chemotherapy including CDDP. CDDP was injected intravenously at 80 mg/m^2 over 1 h on day 1, and other drugs were given on day 2 or later. All patients received uniform hydration and mannitol therapy. Prehydration involved the infusion of 1 l of 5% glucose in normal saline over 4 h. Posthydration was carried out as the infusion of 2 l of 5% glucose in normal saline with 300 ml of 20% mannitol over 6 h. Antiemetic therapy was also uniform. Each patient received 16 mg of dexamethasone and 3 mg of granisetron hydrochloride dissolved in 100 ml of normal saline as an intravenous infusion at 30 min, commencing 30 min before the CDDP infusion. All patients received the infusion at approximately the same time each day.

Specimen collection and assay method

Blood samples of 6 ml were collected from an indwelling heparin-containing catheter placed in the arm opposite to that used for the administration of chemotherapy. Samples were pretreatment, 30 min into the infusion, at the end of the infusion, and at 0.25, 0.5, 1, 2, 4, 8, and 24 h after the infusion. Each sample was centrifuged at 3,000 rpm for 10 min. Plasma was immediately removed and transferred to a polyethylene vial. Approximately 2 ml of the plasma was applied to a Centrifree micropartition system (CF25, Amicon Corp., Tokyo) and centrifuged at 4°C for 20 min. Specimens of plasma and ultrafiltrate were stored at − 20°C until analyzed. Plasma and ultrafiltrate were laid in ashes with nitric acid (80°–100°C) for several hours and then analyzed for platinum (Pt) by inductively coupled plasma spectrometry (Leeman Labs., Inc., Massachusetts, USA). Absorbance was measured at 265.9 nm.

Pharmacokinetic analysis

Modeling of individual concentration data was performed by nonlinear least-squares regression using the program MULTI on a PC-9801 personal computer (NEC, Tokyo) [12]. The best fit was determined by Akaike's information criterion [11]. As a result, plasma concentrations of ultrafilterable platinum (U-Pt) and total plasma platinum (T-Pt) were fit to a one-compartment and to a two-compartment model, respectively. The volume of distribution (Vd), total clearance (Cl), half-life ($t_{1/2}$), and area under the plasma concentration versus time curve (AUC) of U-Pt were calculated. However, for T-Pt we calculated only the AUC, as the estimates of Vd, Cl, and $t_{1/2}$ were unreliable because the plasma concentration remained high (about 30% of the peak plasma concentration) even at the last sampling point (24 h after infusion). The AUC was computed using the trapezoidal rule. The AUCs of T-Pt and U-Pt denote the values for time zero to 24 h and for time zero to infinity, respectively [3].

Statistical analysis

The linear–regression models were constructed by ordinary least squares. In addition, stepwise multivariate regression was performed for the AUC of U-Pt and T-Pt to assess any age effect. Generally, forward stepping was used to select variables. The inclusion criteria for the stepwise procedure was an F value of $\geq$ F(m1, m2) (0.05). Significance was assessed at the 5% level. All statistical analyses were performed using the program STATVIEW (Brainpower Inc., Calabasas, Calif.).

Results

Table 1 summarizes the patients' characteristics. A total of 23 patients were enrolled in the study between September 1993 and February 1994, 8 (34.8%) were $\geq$ 70 years old, and 6 (26.1%) were $\geq$ 75 years old. All patients received combination chemotherapy including CDDP. Only one patient and received chemotherapy including CDDP as prior therapy. Table 2 shows the magnitude of interpatient variability found in both clinical baseline features and pharmacokinetic parameters. There was substantial variation in CDDP pharmacokinetic parameters, especially in the U-Pt $t_{1/2}$ (coefficient of variation, 84%). As compared with the variability of the pharmacokinetic parameters, that of the clinical baseline features was smaller except for GOT and GPT. No significant difference in weight, Ccr, BUN, Cre, GOT, GPT, ICG 15 min, total protein, or albumin was found according to age following regression analysis (data not shown).

We examined the regression analysis of age versus U-Pt and T-Pt pharmacokinetic parameters. Significant correlations between age and the AUC, clearance (Cl), and peak plasma concentration (Cmax) of U-Pt and the AUC of T-Pt were identified (Table 3). Figures 1a and 1b show the relationship between age and the AUC of U-Pt and T-Pt ($r = 0.71$, $P < 0.001$ versus $r = 0.5$, $P = 0.01$), respectively.

The relationships of the clinical baseline features with the AUCs of U-Pt and T-Pt are summarized in Table 4. Of these ten factors, age, GPT, and Cre were significantly (GPT: $r = -0.43$, $P = 0.04$; Cre: $r = 0.42$,

Table 1 Patients' characteristics (*VDS* Vindesine, *MMC* mitomycin C, *VP*-16 etoposide)

Characteristic	Patients ($n = 23$)
Median age (range)	61 (41–80) years
Sex (M/F)	17/6
PS (0/1/2)	5/16/2
Histology (non-small cell/small-cell)	19/4
Stage (III/IV)	8/15
Prior therapy:	
Chemotherapy (CDDP-containing/others)	3(1/2)
Radiation therapy	3
Operation	3
None	14
Chemotherapy received regimen:	
CDDP + VDS + MMC	14
CDDP + VDS	3
CDDP + VP − 16	6

Table 2 Magnitude of interpatient variability in both clinical baseline features and pharmacokinetic parameters (*Cmax* Peak plasma concentration, *CVT* Coefficient of variation)

Factor	Mean	SD	CV%
Clinical baseline features:			
Weight (kg)	57.3	9.2	16.1
ICG15 (%)	8.6	0.8	41.1
GOT(IU/l)	22.1	13.6	61.7
GPT(IU/l)	27.7	25.7	92.8
Total protein (g/dl)	6.9	0.6	8.9
Albumin (g/dl)	3.7	0.5	12.8
BUN (mg/dl)	14.5	3.8	26
Ccr (ml/min)	85.8	20.9	24.4
Cre (mg/dl)	0.7	0.14	20.4
Pharmacokinetic parameters:			
U-Pt AUC	3.05	0.92	30.1
U-Pt Cl	42.4	14.1	33.1
U-Pt Vd	32.6	11.6	35.7
U-Pt $t_{1/2}$	0.58	0.49	84.2
U-Pt Cmax	2.29	0.42	18.3
T-Pt AUC	33.5	7.2	21.4

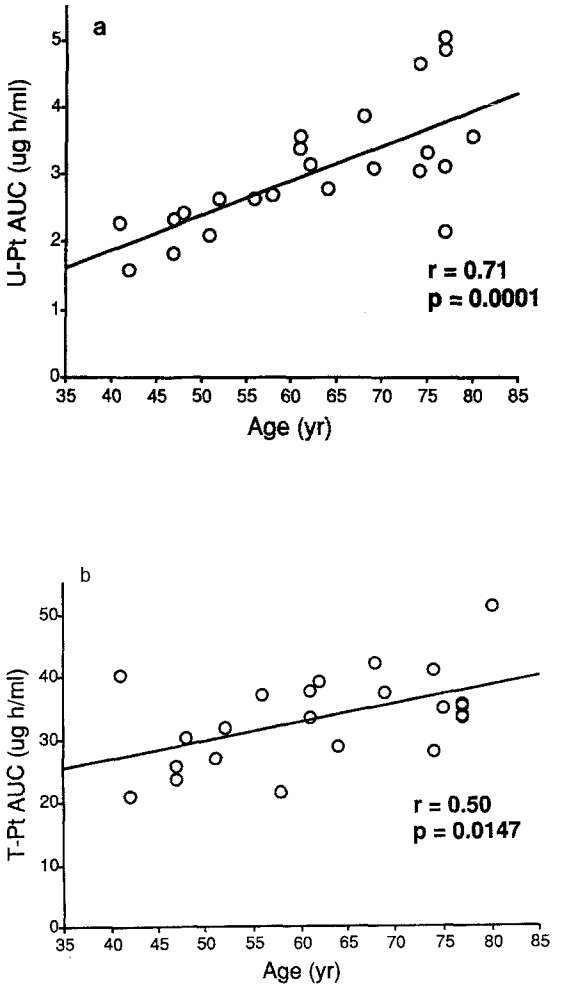

Fig. 1a, b Relationships between age and the AUC of **a** U-Pt and **b** T-Pt. Significant correlations are evident ($r = 0.71$, $P = 0.0001$; $r = 0.5$, $P = 0.0147$, respectively)

Table 3 Correlation between age and pharmacokinetic parameters

Parameter	*P*-value	*r*
U-Pt AUC	0.0001	0.71
U-Pt Vd	0.2456	0.25
U-Pt *t*1/2	0.1302	0.35
U-Pt Cmax	0.0054	0.56
T-Pt AUC	0.0147	0.50

Table 4 Correlation between U-Pt AUC, T-Pt AUC, and clinical conditions: univariate analysis

Factor	U-Pt AUC		T-Pt AUC	
	r	*P* value	*r*	*P*-value
Age	0.71	0.0001	0.50	0.0147
Weight	−0.16	0.4812	−0.10	0.6623
ICG15	0.44	0.0583	0.26	0.2729
GOT	−0.29	0.1757	−0.14	0.5192
GPT	−0.43	0.0404	−0.20	0.3648
Total protein	0.06	0.7829	0.08	0.7173
Albumin	0.12	0.5904	0.21	0.3380
BUN	0.25	0.2552	0.15	0.5061
Ccr	−0.34	0.1262	−0.45	0.3450
Cre	0.42	0.0458	0.65	0.0008

$P = 0.046$) and ICG 15 min, modestly ($r = 0.44$, $P = 0.058$) related to the AUC of U-Pt. On the other hand, age, Ccr, and Cre were significantly related to the AUC of T-Pt (Ccr: $r = -0.45$, $P = 0.035$; Cre: $r = 0.65$, $P = 0.0008$).

Because of multiple correlations existing between demographic variables including age, GPT, Ccr, Cre, and ICG 15 min, stepwise multiple-regression analysis was used to determine the adjusted relationship between age and the AUC of U-Pt or T-Pt. The regression results obtained for the AUC of U-Pt are

Table 5 Stepwise regression of U-Pt AUC[a]

Factor	Coefficient	SE	*F* value
Age	0.045	0.012	13.378

[a]ICG, Cre, and GPT were not significant in the final model. The overall *F* and R^2 values for the model were 13.378 and 0.440

Table 6 Stepwise regression of T-Pt AUC[a]

Factor	Coefficient	SE	*F* value
Age	0.188	0.085	4.907
Cre	27.219	7.841	12.051

[a]Ccr was not significant in the final model. The overall *F* and R^2 values for the model were 11.474 and 0.547

presented in Table 5. The only significant independent predictor was age ($R^2 = 0.66$, *F* value = 13.4). The regression results obtained for the AUC of T-Pt are presented in Table 6. Significant independent predictors included age and Cre. These two factors accounted for 55% of the variability in the AUC of T-Pt data ($R^2 = 0.55$, *F* value = 11.5).

Discussion

Although the numbers of elderly patients who are candidates for chemotherapy are increasing, little information is available concerning the pharmacokinetics and pharmacodynamics of anticancer agents in this group. The effects of ageing on pharmacokinetics are difficult to predict because of the complex physiological changes that accompany the ageing process as well as multiple and variable drug characteristics such as the processes of absorption, distribution, metabolism, and excretion. However, older patients cannot metabolize the drug as efficiently as younger patients because of age-related losses in major organ functions.

Of the CDDP dose, 90% is removed by the kidneys through a combination of glomerular filtration and tubular secretion, and CDDP can bind extensively to plasma proteins [10]. Thus, it is possible that the decreases in renal function and plasma albumin associated with increasing age may influence CDDP pharmacokinetics.

In this study we examined the influence of ageing on CDDP pharmacokinetics in patients with normal renal, hepatic, and bone marrow functions. The results indicate that there is a significant correlation between age and the AUCs of U-Pt and T-Pt in patients with normal organ functions. However, it is not readily apparent whether the change in the AUC is related to the change in age or to other functions. To clarify this point, we evaluated the relationship of the AUC with a number of demographic parameters simultaneously in the context of stepwise multiple-regression analysis. Age was an independent predictor of the AUCs of U-Pt and T-Pt.

Prior to analyzing the relationship between age and CDDP pharmacokinetics, we examined the relationship betweeen age and the clinical baseline features. Although Ccr is generally known to decrease with age, we found no correlation between these two parameters. We think the reason why Ccr was not related to age is that we selected patients whose organ functions, including the kidney function, was normal.

It has recently been suggested that there is a significant correlation between the therapeutic response to CDDP and the AUC of U-Pt [6]. Reece et al. [7] also reported that the Cmax of U-Pt was significantly correlated with the decline in creatinine clearance observed after four courses of CDDP therapy. The present study demonstrates that the AUC and Cmax of U-Pt are significantly correlated with age ($P = 0.0001$, $r = 0.71$; $P = 0.005$, $r = 0.56$, respectively). Therefore, it may be appropriate to reduce the dose or the rate of infusion of CDDP in older patients in proportion to their age.

In conclusion, this study demonstrates that CDDP pharmacokinetic parameters, especially U-Pt, are significantly correlated with age in patients with normal organ function. Further studies will be needed to assess the pharmacodynamic consequences of ageing upon CDDP therapy, but current standards for clinical trial of anticancer agents, which demand combination chemotherapy, confound such pharmacodynamic analysis.

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