Superselective Intra-arterial Infusion Chemotherapy with Nedaplatin for Oral Cancer: A Pharmacological Study of the Dose Clearance

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Abstract

Introduction Nedaplatin (*cis*-diammine-glycolate platinum) is a new anticancer agent developed in Japan. It is especially designed to reduce adverse side effects of CDDP such as renal toxicity and neurotoxicity.

Aim We used nedaplatin as a superselective intra-arterial infusion chemotherapy for oral cancers and carried out a pharmacological study of the dose clearance of nedaplatin based on renal function as well as evaluating its efficacy, including hematological side effects.

Patients and Methods Typical regimens of this chemotherapy consisted of 5-days straight of 24-h continuous intravenous infusion of 5-Fu with a single shot of nedaplatin via transfemoral artery on day 4. The dose of nedaplatin was calculated based on the 24-h creatine clearance. A total of 37 patients who had oral cancer and had received 68 courses (total) of chemotherapy were found to be eligible for this study.

Results Total and free platinum concentrations in the plasma were measured at each of the time points, and the area under the curve (AUC, measured in units of $\mu\text{g h/ml}$) was calculated based on the platinum concentration with the following formula: CL (clearance of free platinum: l/h) = $0.042 \times \text{CCr (ml/min)} + 5.84$. The response rate was 70.1 % (in CR 51 %, in PR 19 %). Histological CR was seen in 28.6 % of surgical specimens. Moderate hematological side effects were seen. However, severe

adverse events were not observed, including those associated with cannulation of the femoral artery.

Conclusion The dose-clearance formula that was established by our study can most likely be utilized to accurately predict the optimal administered dose of nedaplatin for arterial infusion chemotherapy.

Keywords Nedaplatin · Superselective · Intra-arterial infusion · Dose clearance · Chemotherapy

Introduction

Nedaplatin (*cis*-diammine-glycolate platinum, CDGP), that has been developed in Japan, produces anti-tumor effects after uptake into tumor cells by binding to DNA bases and inhibiting DNA replication like cisplatin (CDDP) and carboplatin (CBDCA) [1]. In this respect, this drug has a similar mechanism of action to that of its analogue, cisplatin [2]. CDGP has been reported to have high anti-tumor efficacy in clinical studies against head and neck cancer, esophageal cancer, lung cancer, urologic cancer, and gynecologic cancer [2–9].

Intra-arterial infusion chemotherapy has been used to treat head and neck cancers and has several theoretical advantages when compared with conventional venous infusion chemotherapy. In addition, favorable clinical outcomes have been reported in the literature [10–12]. The greatest advantage of arterial infusion chemotherapy is that higher drug concentrations are obtained at the tumor site while exhibiting only mild systemic toxicity due to relatively low levels of the agent in circulated blood. Both CDDP and CBDCA are clinically used on a regular basis for intra-arterial administration of chemotherapy to cancer patients and there have been several reports regarding

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platinum concentrations in blood and body tissues [11–14]. However, despite these previous studies, the optimal dose for arterial infusion chemotherapy with CDGP is yet to be reported. To minimize side effects and to maximize the effect on cancer cells, it is important that the dose of the anticancer drug be individualized, even in cases where intra-arterial infusion chemotherapy is used. We have pharmacologically investigated the relationship between clearance of CDGP and renal function for this chemotherapy based on the creatinine clearance of oral cancer patients who have undergone superselective intra-arterial chemotherapy using nedaplatin. We also analyzed the correlation between the dose and the AUC (unit: $\mu\text{g h/ml}$) of CDGP administered through intra-arterial infusion.

Materials and Methods

Patients

The eligibility criteria for oral cancer patients who were treated at the Department of Oral and Maxillofacial Surgery, Faculty of Medicine, Kagawa University Hospital were as follows; (1) no prior treatment of cancer, (2) age >20 years, (3) performance status (WHO) 0–2, (4) hematological white blood cells (WBC) >3,000/ μl , platelet count >100,000/ μl .

All patients received the routine medical care specified for cancer treatment, including blood chemistry, cell counts, standard laboratory tests, Chest film, CT, MRI, PET, and Scintigraphy. Creatinine clearance, based on 24-h urine collection, was carefully measured at least twice for each patient before chemotherapy. The value of CCr was adjusted using the following formula

$$\text{CCr (ml/min)} = 24 \text{ h CCr} / (\text{BSA} / 1.48) / 1.44$$

BSA: Body Surface Area (m^2).

Table 1 shows the patient characteristics. Thirty-seven Japanese adult patients (68 courses of chemotherapy) were eligible for this study.

Typical regimens (Table 2) of this chemotherapy consisted of 5 days of 24-h continuous intravenous infusion of 5-Fu (750–1,000 mg/day/body) and a single shot of CDGP on day 4. CDGP was administered via a transfemoral approach using the Seldinger technique (Fig. 1). The routine diagnostic angiographic procedure was accomplished with a standard diagnostic catheter using digital subtraction angiography (DSA), while the vascularity and the extent of the tumor were evaluated with dynamic CT. Typically, blood samples were taken at 8–12 time points after administration of CDGP, as follows: –1, 0, 0.5, 1, 2, 3, 5, 7, 12, 24, 48, 72 h, respectively (Fig. 2). The 0 h refers to

Table 1 Summarized patient data

Patient	n	Age (range)
Male	26	65.0 years (33–92)
Female	11	64.5 years (45–85)
Primary tumor		
Tongue	15	
Gingiva	13	
Floor of mouth	5	
Maxillary sinus	4	
Histology		
SCC	34	
Well	(11)	
Moderate	(15)	
Poor	(2)	
ACC	1	
Other	2	
Stage		
I	3	
II	7	
III	2	
IV	25	
Response rate (CR + PR)	70.1 %	
Histological CR rate	28.6 %	

Table 2 Regimen

DAY	1	2	3	4	5
5-FU 750–1,000 mg/body, cont.iv	↓	↓	↓	↓	↓
Nedaplatin i.a, single shot (133.5 ± 33.1 mg/body)				↓	

the point immediately after completion of the injection. In some cases, after 24 h, further sampling of the blood was not carried out because the platinum concentrations in the plasma were below the lowest detectable level. Total and free platinum concentrations in the plasma were measured, and the AUC ($\mu\text{g h/ml}$) was also calculated based on the platinum concentrations. The total sample number was 684, with 10.1 samples as an average taken from one course of chemotherapy for each patient. The superselective intra-arterial infusion chemotherapy was applied for the purpose of neo-adjuvant and/or induction therapy. Most of the patients who received surgery and/or radiation therapy completely recovered from the hematological nadir caused by the chemotherapy. It is important to point out that among this group there was no concomitant therapy, e.g., irradiation, during the course of chemotherapy. It also should be noted that this study was approved by the ethics committee of our institution and that the written and informed consent of the patients was obtained.

Fig. 1 Intra-arterial chemotherapy for oral cancer by the Seldinger technique. **a** Gingival cancer, T4N1Mo SCC well-differentiated type. Stain solution (indigo-carmin) was injected via a feeding artery to verify the lesion. **b** CT scan, contrast medium was used.

c Angiography at the lesion, which was stained with contrast medium. Arrowheads indicate the lesion, **d** 2 weeks after the chemotherapy, the huge mass on the gingiva had totally disappeared

Fig. 2 Platinum concentrations (CDGP) in the plasma. Almost none of the platinum bound to the protein. CDGP existed in its activated form until elimination

Measurement and Data Analysis

The concentrations of total and free (non-protein bound) platinum in the blood plasma were measured with an atomic absorption spectrometry assay [15] at Shionogi Biochemical Laboratories (Osaka, Japan). The AUC of free platinum was calculated by the trapezoidal method from zero time to the last sampling time [16]. The pharmacokinetics analysis package WinNonlin® Version 2.1 (Pharsight Corporation, California, USA) was used to analyze the AUC.

Table 3 Age parameter value

Patient age (years)	Target AUC (μg h/ml)
50>	20–22
50–70	18–20
70–80	16–18
>80	14–16

Platinum clearance (CL) was obtained using the following formula:

$$CL = \text{Dose (mg)} / \text{AUC (μg h/ml)}$$

APV: Age Parameter Value as a target AUC_{CDGP} was given according to the age of the patient (Table 3). However, the APV number was modified slightly for each patient according to their condition, e.g., physical status, hematological status, and previous medical history.

This formula was correlated with our dose setting for CDGP, and the administered dose was calculated by the following equation. The AUC of CDGP was estimated as being four times the AUC of CBDCA based on several studies [17–19], leading to the following adjusted equation for the Age Parameter Value.

$$\text{Dose (mg: CDGP)} = \text{APV} \times [\text{CCr (ml/min)} + 25] / 16$$

Results

Table 1 shows the patients' details, including tumor type, histology, stage, and grade. The average age of the

patients' was 65 years, with 92 % of the tumors being squamous cell carcinoma as determined by histology. The overall response rate for the arterial infusion chemotherapy was 70.1 %. Histological CR was seen in 28.6 % of surgical specimens. In no cases adverse side effects beyond those of grade 4 (CTCAE Version 3. NCI, 2003) were observed. Table 4 summarizes the measurements obtained, including the AUC. A total of 684 samples were obtained during 68 courses of chemotherapy in 37 patients. The average administered dose of CDGP was 133.5 ± 33.1 mg (mean $\pm$ SD). The AUC ratio, based on the total platinum AUC compared to the AUC from free platinum, was 73.7 %. Within 24 h, all platinum in the plasma had been eliminated in all of the patients. Table 5 shows the data of hematological toxicity related to this chemotherapy. As can be seen, both WBC and platelets decreased significantly after the chemotherapy, and hemoglobin also decreased, though not significantly. This chemotherapy had no adverse effects on renal function (Table 6).

In this study, the patient age showed a significant negative correlation with creatinine clearance (CCr) ($r = 0.522$, p value for slope <0.001) and clearance of free platinum (CL) from CDGP ($r = 0.409$, p value for slope <0.001) (Fig. 3A, B). BSA (m^2) did not show a significant co-relationship ($r = 0.219$, p value for slope >0.001) with CL or with CCr ($r = 0.046$, p value for slope = 0.011) (Fig. 3C). The administered dose was calculated based on CCr and the patient's age. The final measured AUC based on free platinum showed a significant relationship with

dose ($r = 0.493$, p value for slope <0.001), as seen in Fig. 4. Figure 5 shows the relationship between CL and CCr and dose. CL showed a significant correlation with both CCr ($r = 0.447$, p value for slope <0.001) and dose ($r = 0.467$, p value for slope <0.001). The AUC based on free platinum showed a correlation with CCr (Fig. 5c). Results as a regression analysis for correlation with clearance of free platinum and CCr led to the following formulas:

$$\text{CL (clearance of free platinum:l/h)} = 0.042 \times \text{CCr} \\ (\text{ml/min}) + 5.84$$

$$\text{Dose (mg)} = \text{AUC } (\mu\text{g h/ml}) \times (0.042 \times \text{CCr} \\ (\text{ml/min}) + 5.84)$$

Discussion

When an anti-tumor drug is given by venous administration, it is diluted during circulation. In addition, some parts of the drug are metabolized or eliminated before reaching the tumor. In contrast, when the drug is given by intra-arterial infusion, the drug bypasses the hepatic metabolism and directly enters the tumor tissue. Higher drug concentrations may therefore be obtained because the drug is directly injected into the arteries feeding the tumor. It is well known that anti-tumor efficacy is closely related to drug concentrations in the tumor [20]. However, it is also a fact that tumor drug concentrations resulting from intra-arterial infusion might easily be affected by a number of factors. These include the distribution of the feeding arteries that are chosen, the infusion time, blood inflow and outflow rates, and the size and location of the tumor. Therefore, it may be difficult to predict with accuracy the platinum concentrations in the tumor tissue when given via

Table 4 Measured data

Number of courses	68
Total number of samples	684 (10.1 samples per 1 course)
Average BSA (m^2)	1.52 ± 0.14
Dose (mg)/body	133.5 ± 33.1 (50–220)
Infusion time (min)	59.67 (20–140)
AUC total platinum ($\mu\text{g h/ml}$) $\pm$ SD	19.07 ± 5.39
AUC free platinum ($\mu\text{g h/ml}$) $\pm$ SD	14.23 ± 3.58
Cmax total platinum ($\mu\text{g/ml}$) $\pm$ SD	5.56 ± 1.59
Cmax free platinum ($\mu\text{g/ml}$) $\pm$ SD	4.91 ± 1.24

Table 5 Hematological toxicity

	White blood cell	Hemoglobin	Platelet
Pre-chemotherapy (mean $\pm$ SD)	$4,988 \pm 1,923$ (μl)	12.9 ± 2.4 (g/dl)	23.9 ± 4.1 ($\times 10^4/\mu\text{l}$)
Post-chemotherapy (mean $\pm$ SD)	$3,022 \pm 1,054$ (μl)	10.9 ± 1.8 (g/dl)	13.1 ± 3.1 ($\times 10^4/\mu\text{l}$)
Decreasing rate (mean $\pm$ SD)	$39.4 \pm 22.9^*$ (%)	$15.4 \pm 10.6^{**}$ (%)	$45.7 \pm 21.9^*$ (%)
Nadir after chemotherapy (days)	22.2 ± 5.4	20.7 ± 4.8	19.5 ± 6.2

t test, * $p < 0.05$, ** $p > 0.05$

Table 6 Renal function

Pre-chemotherapy CCr (ml/min) $\pm$ SD	$92.35 \pm 27.27^*$
Post-chemotherapy CCr (ml/min) $\pm$ SD	$89.84 \pm 27.83^*$

* n.s

Fig. 3 **A** Relation to Patient age and CCr, **B** Relation to Patient age and CDGP clearance, **C** Relation to BSA and CDGP clearance

arterial infusion. Nonetheless, it can be predicted with relative certainty that platinum concentrations in the tumor tissue, when the platinum is administered by superselective intra-arterial infusion, are likely to be much higher than with the dosage given by conventional venous infusion. In fact, in some studies using CDDP and CBDCA it has been reported that platinum concentrations in the tumor with intra-arterial infusion are 2–7 times higher than in similar tumors given the same chemotherapeutic agent via

Fig. 4 Relation to Dose and AUC

intravenous infusion. This result is concomitant with a relatively higher response rate [19, 21]. In clinical settings, both CDDP and CBDCA have been used as drugs for arterial chemotherapy with favorable results reported [10–12, 14, 22]. However, there is little data regarding intra-arterial infusion chemotherapy with CDGP. With regard to dose-clearance studies including AUC with CDGP, several reports on the clinical base have been published [9, 23, 24]. Ishibashi et al. [24] have reported a formula for predicting the optimal dosage of CDGP based on renal function for conventional intravenous chemotherapy. They found that only creatinine clearance is a significant covariate of the clearance of CDGP, a finding that is supported by our study. This formula was developed based on a large number of Japanese cancer patients who had cancer in different organs throughout the body and patient data that were obtained from multiple institutions in Japan. In contrast, there is little basis for comparison between these two formulas due to the fact that our formula was established using data from intra-arterial infusion chemotherapy. It has been reported that the platinum concentrations in plasma and the AUC of free platinum by intravenous infusion are significantly different from those with intra-arterial infusion, even when the same doses are given [19, 25].

CDGP has a short elimination half-life (1.1–4.4 h) and a pharmacokinetic profile very similar to that of CBDCA [18, 26]. The limiting factor of CDGP is thought to be hematological toxicity, which has also been found with CBDCA. We tried to modify the formula that Calvert et al. [27] developed for CBDCA in order to determine the optimal dose for CDGP. The anti-tumor activity and pharmacokinetics of CDGP in comparison with CDDP and CBDCA have been previously reported [18]. In these articles [17–19], the anti-tumor activity and the AUC for free platinum of CDGP were reported to be 3.6–4 times higher than those of CBDCA when compared with the same dose. Therefore, we used the following formula to

Fig. 5 **A** Relation to CCr and CDGP clearance, **B** Relation to Dose and CDGP clearance, **C** Relation to CCr and Free AUC

adjust the administered dose of CDGP for intra-arterial infusion chemotherapy:

$$\text{APV: Age Parameter Value as a target AUC}_{\text{CDGP}} = \text{target AUC}_{\text{CBDCA}} \times 4$$

The target AUC was determined based on the patient's age due to its linear relationship with the physiological status and tolerance for anti-tumor agents. In fact, in our study the patient's age showed a significant correlation with both creatinine clearance and clearance of CDGP. For

conventional intravenous chemotherapy, the range from 80 to 100 mg/m² of CDGP is recommended according to the results of clinical trials [5, 28, 29]. The dose administered is determined based on the body surface area (BSA: m²). If a dose based on BSA is applied, the administered dose ranges from 121.6 mg (80 mg/m²) up to 152.0 mg (100 mg/m²) per body. The average dose calculated based on the 24-h CCr in this study was 133.5 mg per body, which is almost at the center of the range of the BSA-based dose setting. However, for each individual, the actual dose administered was not totally correlated to the BSA base dose. According to the results of our study, BSA seems to be a relatively poor index when used for determining dose because BSA does not show a statistically significant correlation with the clearance of CDGP ($r = 0.046$, $p \text{ value} = 0.01149 > 0.01$). In addition, BSA did not show any significant correlation with creatinine clearance. Finally, it would presumably be difficult to predict the side effects (e.g., hematological toxicity and gastrointestinal disturbance) individually after administration with a dosage based solely on BSA. For CBDCA, the relationship between the AUC, anti-tumor activity, and side effects has been investigated thoroughly [30–32]. The AUC of CDGP should also be a useful index for the purpose of predicting not only anti-tumor activity, but also other adverse side effects. It has been reported that the AUC of CDGP has a significant co-relationship to thrombocytopenia [23, 33]. Therefore, it is reasonable to conclude that the AUC should be optimized and individualized for patients being administered chemotherapy, even in cases where intra-arterial infusion is used. If one can estimate the AUC of CDGP, it may then be possible to predict both the efficacy of the course of chemotherapy and the adverse side effects with a relatively high level of accuracy. However, we will need to evaluate the details of the relationship of the individualized AUC_{CDGP} and the efficacy in relation to adverse effects in a future study.

In our results, a certain level of myelosuppression, e.g., leukocytopenia or thrombocytopenia, was observed. Its occurrence seemed to be within a modest and acceptable range compared to conventional chemotherapy with nedaplatin [5, 6, 8, 28, 29, 34]. In addition, we found no statistical significant adverse effect with regard to the concentrations of hemoglobin and renal function in pre-versus post-chemotherapy. In particular, with regard to preserving renal function, it should be noted that our superselective intra-arterial chemotherapy with a CDGP dose setting based on renal function most likely can minimize renal toxicity.

In conclusion, the dose-clearance formula that was established by our study can most likely be utilized to accurately predict the optimal administered dose of CDGP. This formula is based on the creatinine clearance of the

cancer patient, allowing the clearance of CDGP to be estimated and individualized in terms of the dose. Although further clinical studies may be necessary in order to fully investigate the relationship between the AUC of CDGP and the side effects using superselective intra-arterial infusion chemotherapy, our current findings remain quite promising. However, we also should note that it will be most critical to investigate how to influence the 5–10 year survival rates of patients finally with our superselective intra-arterial infusion chemotherapy with CDGP.

References

1. Drobnik J (1983) Antitumor activity of platinum complexes. *Cancer Chemother Pharmacol* 10:145–149
2. Suzumura Y, Kato T, Ueda R, Ota K (1989) Effect of treatment schedule on antitumor activity of glycolate-O,O'-diammineplatinum(II), a new platinum derivative: comparison with *cis*-diamminedichloroplatinum(II). *Anticancer Res* 9:1083–1088
3. Inuyama Y, Miyake H, Horiuchi M, Hayasaki K, Komiyama S, Ota K (1992) A late phase II clinical study of *cis*-diammine glycolato platinum, 254-S, for head and neck cancers. *Gan To Kagaku Ryoho* 19:871–877
4. Inuyama Y, Miyake H, Horiuchi M, Hayasaki K, Komiyama S, Ota K (1992) An early phase II clinical study of *cis*-diammine glycolato platinum, 254-S, for head and neck cancers. *Gan To Kagaku Ryoho* 19:863–869
5. Sasaki Y, Amano T, Morita M, Shinkai T, Eguchi K, Tamura T, Ohe Y, Kojima A, Saijo N (1991) Phase I study and pharmacological analysis of *cis*-diammine(glycolato)platinum (254-S; NSC 375101D) administered by 5-day continuous intravenous infusion. *Cancer Res* 51:1472–1477
6. Fukuda M, Shinkai T, Eguchi K, Sasaki Y, Tamura T, Ohe Y, Kojima A, Oshita F, Hara K, Saijo N (1990) Phase II study of (glycolate-O,O') diammineplatinum(II), a novel platinum complex, in the treatment of non-small-cell lung cancer. *Cancer Chemother Pharmacol* 26:393–396
7. Kanzawa F, Matsushima Y, Nakano H, Nakagawa K, Takahashi H, Sasaki Y, Saijo N (1988) Antitumor activity of a new platinum compound (glycolate-O,O') diammineplatinum (II) (254-S), against non-small cell lung carcinoma grown in a human tumor clonogenic assay system. *Anticancer Res* 8:323–327
8. Akaza H, Togashi M, Nishio Y, Miki T, Kotake T, Matsumura Y, Yoshida O, Aso Y (1992) Phase II study of *cis*-diammine(glycolato)platinum, 254-S, in patients with advanced germ-cell testicular cancer, prostatic cancer, and transitional-cell carcinoma of the urinary tract. 254-S Urological Cancer Study Group. *Cancer Chemother Pharmacol* 31:187–192
9. Maruoka Y, Ando T, Ogiuchi Y, Ogiuchi H (2007) Nedaplatin (NDP)-combination therapy (NDP/5-FU, NDP/S-1) for oral cancer. *Gan To Kagaku Ryoho* 34:713–717
10. Ishii A, Korogi Y, Nishimura R, Kawanaka K, Yamura M, Ikushima I, Hirai T, Yamashita Y, Shinohara M (2004) Intraarterial infusion chemotherapy for head and neck cancers: evaluation of tumor perfusion with intraarterial CT during carotid arteriography. *Radiat Med* 22:254–259
11. Fuwa N, Ito Y, Matsumoto A, Kamata M, Kodaira T, Furutani K, Sasaoka M, Kimura Y, Morita K (2000) A combination therapy of continuous superselective intraarterial carboplatin infusion and radiation therapy for locally advanced head and neck carcinoma. Phase I study. *Cancer* 89:2099–2105
12. Sileni VC, Fossier V, Maggiani P, Padula E, Beltrame M, Nicolini M, Arslan P (1992) Pharmacokinetics and tumor concentration of intraarterial and intravenous cisplatin in patients with head and neck squamous cancer. *Cancer Chemother Pharmacol* 30:221–225
13. Sculier JP, Paesmans M, Thiriaux J, Lecomte J, Bureau G, Giner V, Koumakis G, Lafitte JJ, Berchier MC, Alexopoulos CG, Zacharias C, Mommen P, Ninane V, Klastersky J (1999) A comparison of methods of calculation for estimating carboplatin AUC with a retrospective pharmacokinetic-pharmacodynamic analysis in patients with advanced non-small cell lung cancer. European Lung Cancer Working Party. *Eur J Cancer* 35:1314–1319
14. Kanamori Y, Kigawa J, Minagawa Y, Irie T, Itamochi H, Cheng X, Okada M, Terakawa N (1997) Clinical responses and platinum concentrations in tumors after intra-arterial and intravenous administration of cisplatin in the same patients with cervical cancer. *Gynecol Obstet Investig* 44:57–60
15. LeRoy AF, Wehling ML, Sponseller HL, Friauf WS, Solomon RE, Dedrick RL, Litterst CL, Gram TE, Guarino AM, Becker DA (1977) Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry. *Biochem Med* 18:184–191
16. Gabrielsson J, Weiner D (1998) Pharmacokinetic and pharmacodynamic data analysis: concept & applications, 3rd edn. Swedish Pharmaceutical Press, Stockholm, pp 141–147
17. Sasaki Y, Shinkai T, Eguchi K, Tamura T, Ohe Y, Ohmori T, Saijo N (1991) Prediction of the antitumor activity of new platinum analogs based on their ex vivo pharmacodynamics as determined by bioassay. *Cancer Chemother Pharmacol* 27:263–270
18. Sasaki Y, Tamura T, Eguchi K, Shinkai T, Fujiwara Y, Fukuda M, Ohe Y, Bungo M, Horichi N, Niimi S et al (1989) Pharmacokinetics of (glycolate-0,0')-diammine platinum (II), a new platinum derivative, in comparison with cisplatin and carboplatin. *Cancer Chemother Pharmacol* 23:243–246
19. Kigawa J, Minagawa Y, Itamochi H, Kanamori Y, Ishihara H, Terakawa N (1995) Platinum concentrations in uterus and serum after internal iliac arterial infusion of platinum compounds in rabbits. *Obstet Gynecol* 86:265–268
20. Frei E 3rd, Canellos GP (1980) Dose: a critical factor in cancer chemotherapy. *Am J Med* 69:585–594
21. Szluha K, Uzonyi I, Bascso J, Lampe L, Czifra I, Peter M, Vilena C, Schmidt W (1995) Determination of Pt concentration in cervical tumor-tissues using energy-dispersive X-ray fluorescence (EDXRF) method. *Microchem J* 51:238–244
22. Imai S, Kajihara Y, Munemori O, Kamei T, Mori T, Handa T, Akisada K, Orita Y (1995) Superselective cisplatin (CDDP)-carboplatin (CBDCA) combined infusion for head and neck cancers. *Eur J Radiol* 21:94–99
23. Ishibashi T, Yano Y, Oguma T (2005) Determination of optimal dosage for nedaplatin based on pharmacokinetic and toxicodynamic analysis. *Anticancer Res* 25:1273–1281
24. Ishibashi T, Yano Y, Oguma T (2002) A formula for predicting optimal dosage of nedaplatin based on renal function in adult cancer patients. *Cancer Chemother Pharmacol* 50:230–236
25. Itamochi H, Kigawa J, Minagawa Y, Cheng X, Okada M, Terakawa N (1997) Antitumor effects of internal iliac arterial infusion of platinum compounds in a rabbit cervical cancer model. *Obstet Gynecol* 89:286–290
26. Ota K, Oguma T, Shimamura K (1994) Pharmacokinetics of platinum in cancer patients following intravenous infusion of *cis*-diammine(glycolato)platinum, 254-S. *Anticancer Res* 14:1383–1387
27. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E (1989)

- Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 7:1748–1756
28. Kurita H, Yamamoto E, Nozaki S, Wada S, Furuta I, Kurashina K (2004) Multicenter phase I trial of induction chemotherapy with docetaxel and nedaplatin for oral squamous cell carcinoma. *Oral Oncol* 40:1000–1006
29. Fuwa N, Kodaira T, Kamata M, Matsumoto A, Furutani K, Tachibana H, Ito Y (2002) Phase I study of combination chemotherapy with 5-fluorouracil (5-FU) and nedaplatin (NDP): adverse effects and recommended dose of NDP administered after 5-FU. *Am J Clin Oncol* 25:565–569
30. Duffull SB, Robinson BA (1997) Clinical pharmacokinetics and dose optimisation of carboplatin. *Clin Pharmacokinet* 33:161–183
31. Okamoto H, Nagatomo A, Kunitoh H, Kunikane H, Watanabe K (1998) Prediction of carboplatin clearance calculated by patient characteristics or 24-hour creatinine clearance: a comparison of the performance of three formulae. *Cancer Chemother Pharmacol* 42:307–312
32. Oya R, Nakamura S, Ikemura K, Takagi S, Mugino H (2004) AUC of Calvert's formula in targeted intra-arterial carboplatin chemoradiotherapy for cancer of the oral cavity. *Br J Cancer* 90:2062–2066
33. Ohbayashi Y, Miyake M, Iwasaki A, Ogawa T, Nagahata S, Toyama Y, Ohkawa M (2004) Clinical study for determination of the dosage formula for intra-arterial infusion chemotherapy with nedaplatin. *Gan To Kagaku Ryoho* 31:713–716
34. Ita M, Okafuji M, Fukuda K, Mitsuoka K, Hanakita T, Hayatsu Y (2003) Concurrent chemoradiotherapy with new platinum compound nedaplatin in oral cancer. *Oral Oncol* 39:144–149