JPP Journal of Pharmacy and Pharmacology

JPP 2009, 61: 615–621

Received September 11, 2008
Accepted January 19, 2009
DOI 10.1211/jpp/61.05.0010
ISSN 0022-3573

Research Paper

Influence of dosing schedules on toxicity and antitumour effects of combined cisplatin and docetaxel treatment in mice

Ayumi Kodama[a], Hideto To[b], Tomohiro Kinoshita[a], Ichiro Ieiri[a] and Shun Higuchi[a]

[a]Clinical Pharmacokinetics, Division of Clinical Pharmacy, Department of Medico-Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka and [b]Department of Hospital Pharmacy, Nagasaki University Hospital of Medicine and Dentistry, Nagasaki, Japan

Abstract

Objectives The combination of cisplatin and docetaxel shows a better cure rate against non-small-cell lung cancer than other drug combinations in clinical studies; however, severe myelosuppression and nephrotoxicity are dose-limiting factors. The purpose of this study was to establish a suitable dosing schedule to reduce adverse effects and improve the antitumour effects.

Methods Cisplatin and docetaxel were administered i.p. to male ICR mice simultaneously, or sequentially with either cisplatin or docetaxel first followed by the second drug 12 h later (docetaxel–cisplatin and cisplatin–docetaxel groups). Antitumour effects of these schedules were also tested in C57BL/6N mice bearing Lewis lung carcinomas.

Key findings The simultaneous docetaxel/cisplatin group showed the lowest survival rate and the highest blood urea nitrogen (BUN) concentration. Cisplatin concentrations in the plasma and kidney were higher in the simultaneous dosing group than the sequential dosing groups. Antitumour effect was the greatest in the docetaxel–cisplatin group.

Conclusions The docetaxel–cisplatin regimen inhibited tumour growth the best and reduced mortality and nephrotoxicity.

Keywords cisplatin; combined therapy; docetaxel; dosing interval; dosing sequence

Introduction

The combination of cisplatin and docetaxel has a high therapeutic effect against non-small-cell lung cancer (NSCLC).[1,2] However, the combination of cisplatin and docetaxel causes severe myelosuppression and peripheral nerve injury, limiting its clinical use in many patients with NSCLC.[3,4] Moreover, nephrotoxicity caused by cisplatin is a dose-limiting factor,[5,6] when used alone and in combination with docetaxel.[4] Many studies have attempted to decrease cisplatin-induced nephrotoxicity using anti-oxidising agents.[7–9] Protocols in previous clinical studies have almost always administered cisplatin 1 h after an infusion of docetaxel.[3,4] However, there has been little research into the dosing schedule for cisplatin and docetaxel in combination in terms of interval and sequence.

In preliminary studies of adriamycin and docetaxel in mice we found that modifying the dosing sequence and the dosing time not only significantly reduced leucopenia and toxic death but also significantly improved inhibition of tumour growth compared with simultaneous administration of the drugs, as commonly used in clinical practice.[10–12] A remarkable result in these studies was that toxic death was markedly reduced in the group that were given adriamycin 12 h after docetaxel injection compared with all the other co-administration groups.[10,12] In other combination therapies, adverse effects and antitumour effects vary according to the dosing interval and dosing sequence.[13,14] The dosing schedule for cisplatin and docetaxel injections in terms of dosing interval and sequence has not been examined in detail. We therefore investigated whether modifying the dosing schedule can reduce severe adverse effects and improve antitumour effect. We analysed the pharmacokinetics of cisplatin and docetaxel to clarify the mechanisms underlying the effects of dosing schedule on pharmacological actions.

Correspondence: Hideto To PhD, Department of Hospital Pharmacy, Nagasaki University Hospital of Medicine and Dentistry, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan. E-mail: hide-to@umin.net

Materials and Methods

Animals and tumour cell line

Male ICR (5 weeks old) and C57BL/6N (4 weeks old) mice were purchased from Charles River Japan, Inc. (Kanagawa, Japan). Mice were housed 6–9 per cage under standardised light–dark cycle conditions (lights on and off at 7:00 and 19:00, respectively) at a room temperature of 22 ± 1°C and humidity of 60 ± 10%, with free access to food and water. Experiments were performed after formal approval by the Institutional Ethical Committee for Research on Animals.

Lewis lung carcinoma (LLC) cells were purchased from Dainippon Sumitomo Pharma Co., Ltd (Osaka, Japan). LLC cells were maintained in Dulbecco's modified Eagle's medium (high-glucose) supplemented with 10% fetal bovine serum and 0.05% kanamycin, penicillin and streptomycin in a humidified atmosphere of 95% air and 5% CO_2 at 37°C.

LCC cells (3×10^6 cells) were transplanted into the subcutaneous tissue of mice 4 days before drug injection.

Drugs

Cisplatin (supplied by Nippon Kayaku Co. Ltd Tokyo, Japan) was dissolved in saline and the solution sonicated for 20 min (final concentration: 0.75 mg/ml). Docetaxel (purchased from Sanofi-Aventis, Tokyo, Japan) was dissolved in 95% ethanol and diluted with 5% glucose solution.

Cisplatin (7.5 mg/kg) and docetaxel (12.5 mg/kg) were injected i.p. to ICR mice. Mice were divided into four groups. Those in the simultaneous dosing group (docetaxel/cisplatin) were given both drugs simultaneously. The sequential dosing groups (cisplatin–docetaxel and docetaxel–cisplatin) were given the second drug 12 h after the first. Controls were given vehicle (ethanol–glucose solution).

Determination of antitumour effect

Four days after subcutaneous inoculation of LLC (3×10^6 cells) into C57BL/6N mice, mice ($n = 14$ per group) were given two cycles of cisplatin and docetaxel 7 days apart. Control mice ($n = 13$) received no treatment.

Tumour dimensions was measured using Vernier callipers and the tumour weight (mg) was calculated once every 2 days according to the following equation: tumour weight = $A \times B^2/2$, where A is the longer dimension and B the shorter dimension (mm). Relative tumour growth was expressed as the change in tumour volume from the initiation of drug injections.

Determination of tolerance (survival)

To determine toxic death, seven cycles of cisplatin and docetaxel were administered at 7 day intervals (total of 52.5 mg/kg cisplatin and 87.5 mg/kg docetaxel) ($n = 14$ or 15). Survival time was recorded for 49 days.

Measurement of leucocyte count

Blood samples were withdrawn from the orbital sinus 3 days after single or three-times-weekly injections of drugs in the four groups ($n = 9$–12). Leucocyte counts were measured immediately after blood sampling using an automatic leucocyte counter.

Measurement of blood urea nitrogen (BUN)

Four cycles of drugs were administered at 7-day intervals ($n = 13$–16). To estimate its renal toxicity when administered alone, cisplatin (7.5 mg/kg i.p.) was injected into ICR mice.

Blood samples were withdrawn from the orbital sinus on days 5, 12 and 26 after the first drug administration. All blood samples were centrifuged immediately at 3000*g* for 15 min at 15°C, and then the plasma frozen at −80°C until assay. BUN was measured using a commercial kit (Wako Pure Chemical Industries Ltd, Osaka, Japan).

Pharmacokinetics

In mice treated every 7 days for four cycles, blood samples were obtained via the orbital sinus at the following time points after drug injection: 4 h after each docetaxel injection in the three docetaxel-treated groups on days 0, 7 and 21 ($n = 4$–9); 4 h after each cisplatin injection in the three cisplatin-treated groups on days 0, 7 and 21 ($n = 6$–9).

The right kidney was removed under ether anaesthesia 4 h (day 0) after a single administration of drugs ($n = 8$) and 4 h (days 7 and 21) after twice- or four-times-weekly injections of drugs ($n = 8$). Blood samples were centrifuged immediately at 3000*g* for 15 min at 15°C. Plasma and kidneys were frozen at −80°C until assay.

Docetaxel concentrations in plasma were quantified by an HPLC method with UV detection, as described previously.[10] Cisplatin levels were determined from platinum (Pt) concentrations in the kidney and blood.

Plasma (40 μl) was added to 248 μl 1% Triton X-100 and 32 μl 1 M HCl, and the concentration of Pt measured.

The kidney was weighed and treated with 2 ml 60% nitric acid until completely digested. The solution was added to 248 μl 1% Triton X-100 and 32 μl 1 M HCl to determine the Pt concentration.

Pt was determined on a 20-μl sample by flameless atomic absorption spectrophotometry using Zeeman effect correction (Hitachi Polarized Zeeman AAS Model Z-9000; Hitachi, Hitachi City, Japan) under the following conditions: lamp current 12.5 mA; wave length 265.9 nm; slit width 0.40 nm.

Statistical analysis

Survival was plotted using the Kaplan–Meier method and compared by the log-rank test. Leucocyte count, BUN levels and drug concentrations are given as means ± SD. All other values are given as means ± SE.

Groups were compared by one-way analysis of variance (ANOVA) and repeated ANOVA, and differences between groups were determined by Scheffe's test. Statistical moment analysis was performed by calculating pharmacokinetic parameters such as area under the plasma–time concentration curve (AUC).

A P value of less than 0.05 was considered significant.

Results

Influence of dosing schedule on adverse effects

After repeated cisplatin and docetaxel administration, the survival rates on day 49 were 0% in the docetaxel/cisplatin group, 57.1% in the cisplatin–docetaxel group and 53.3% in

the docetaxel–cisplatin group (Figure 1). The two sequential-treatment groups showed significantly better survival than the docetaxel/cisplatin group (both $P < 0.05$).

Leucocyte counts were significantly lower in the drug-treated groups compared with the control group on days 3 and 17 ($P < 0.05$; Figure 2). There was no difference in leucocyte counts between the drug-treated groups.

After a single drug administration, there was no difference in BUN level between the treatment groups on day 5 (Figure 3). When drugs were administered repeatedly, the BUN concentration in the docetaxel/cisplatin group increased gradually, and was significantly higher in the docetaxel/cisplatin group than in the control group on day 26 ($P < 0.05$; Figure 3). However, almost no mice in the cisplatin alone, cisplatin–docetaxel and docetaxel–cisplatin groups showed an increase in BUN.

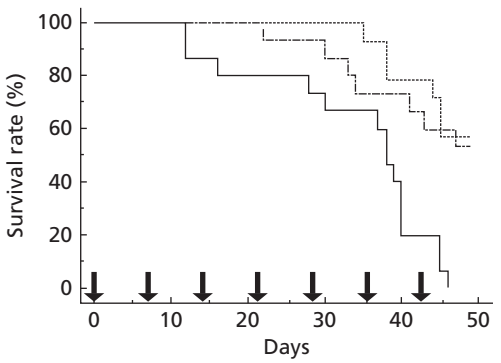

Figure 1 Influence of dosing schedule on survival rate during the combined administration of cisplatin and docetaxel in ICR mice. Cisplatin (CIS; 7.5 mg/kg i.p.) and docetaxel (DOC; 12.5 mg/kg i.p.) were administered every 7 days simultaneously (DOC/CIS: $n = 15$; solid lines) or sequentially, 12 h apart: DOC–CIS ($n = 14$; dashed line) and CIS–DOC ($n = 14$; dotted line). The arrows show when drugs were administered.

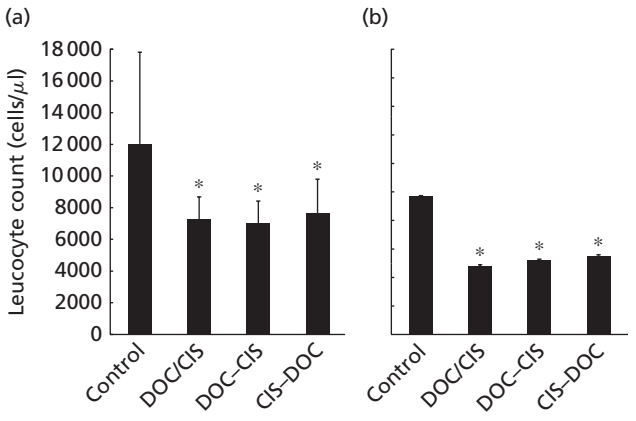

Figure 2 Influence of dosing schedule on myelosuppression. Leucocyte counts were measured on days (a) 3 and (b) 17 during the combined administration of cisplatin (CIS; 7.5 mg/kg i.p.) and docetaxel (DOC; 12.5 mg/kg i.p.) in ICR mice ($n = 9$–12). Vehicle was administered to the control group ($n = 10$–13). Values are means ± SD. *$P < 0.05$ vs control group.

Influence of dosing schedule on pharmacokinetics

Plasma docetaxel concentrations were measured 4 h after docetaxel injection in mice given repeated administration of cisplatin and docetaxel. There were no significant differences in docetaxel levels between the groups on days 0, 7 and 21 (Figure 4).

Plasma cisplatin concentrations were measured at 4 h after cisplatin injection in mice given repeated injections of cisplatin and docetaxel. Only the docetaxel/cisplatin group showed an increase in cisplatin concentration compared with day 0. On day 21, the cisplatin concentration was significantly higher in the docetaxel/cisplatin group than in the docetaxel–cisplatin and cisplatin–docetaxel groups ($P < 0.05$; Figure 5).

Kidney cisplatin concentrations measured 4 h after cisplatin injection in mice given repeated administration of cisplatin and docetaxel were markedly higher in the docetaxel/cisplatin group than in the cisplatin–docetaxel group on day 21 ($P < 0.05$, Figure 6).

Influence of dosing time on tumour growth after combination of cisplatin and docetaxel

Tumour growth was inhibited in all treated groups compared with the control group (all $P < 0.05$; Figure 7).

Discussion

Survival rates in the intermittent dosing groups (cisplatin–docetaxel and docetaxel–cisplatin), in which the second drug was administered 12 h after the first, were increased significantly by about 50% compared with the simultaneous dosing (docetaxel/cisplatin) regimen commonly used in clinical practice. Toxic death caused by administration of antitumour drugs in rodents is generally thought to relate to severe myelosuppression and drug-dependent organic injury. Leucocytes were significantly decreased in all the drug-treated groups compared with the control group. There were no significant differences in leucocyte counts between the drug-treated groups, even though lethal toxicity was significantly higher in the the docetaxel/cisplatin group than the cisplatin–docetaxel and docetaxel–cisplatin groups. Cisplatin is known to be nephrotoxic, and severe renal toxicity is potentially fatal.[5,6] In the present study, rapid augmentations in BUN were observed in all deceased mice. BUN levels increased in the docetaxel/cisplatin group compared with the control group with every cisplatin administration. On other hand, BUN concentrations above 42.4 mg/dl were seen in 5 of 16 mice in the docetaxel–cisplatin group and 4 of 15 mice in the cisplatin–docetaxel group; almost all mice in both dosing groups showed BUN levels about equal to the control group. Previous studies have reported that toxic death could be markedly decreased by inhibiting cisplatin-induced nephrotoxicity.[15,16] These results suggest that relieving cisplatin-induced renal toxicity contributes significantly to the improved survival rate in the sequential dosing groups compared with the simultaneous dosing group.

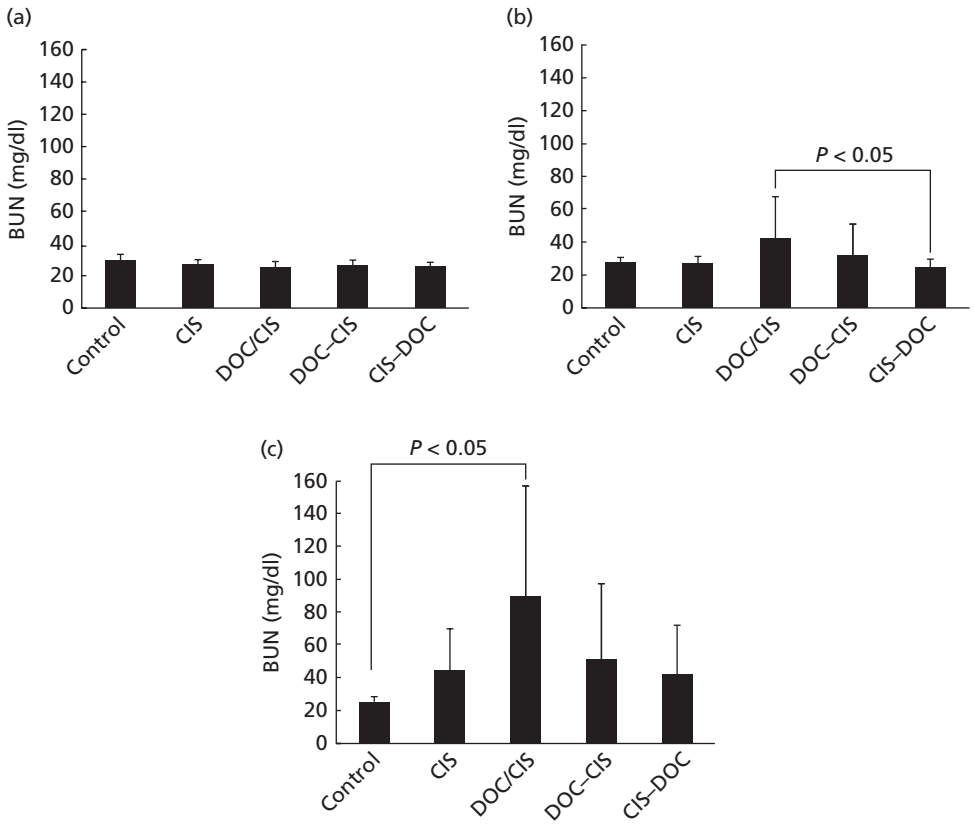

Figure 3 Influence of dosing schedule on blood urea nitrogen (BUN) on days (a) 5 (b) 12 and (c) 26. Levels of BUN were measured during administration of cisplatin (CIS; 7.5 mg/kg, i.p.) and/or docetaxel (DOC; 12.5 mg/kg, i.p.) in ICR mice (n = 14–16). Vehicle was administered to the control group (n = 10). Values are means ± SD.

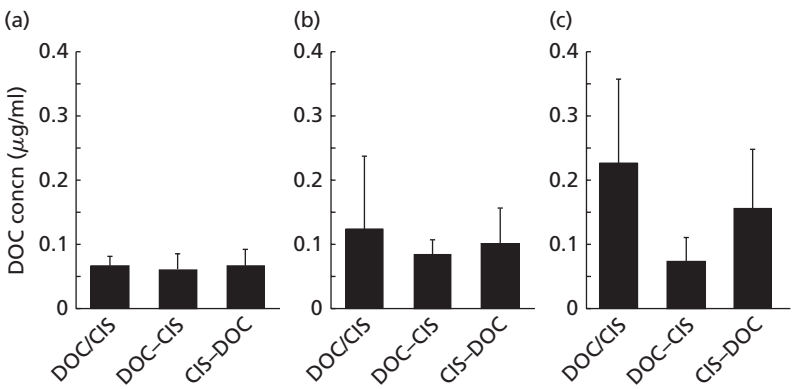

Figure 4 Influence of dosing schedule on plasma docetaxel concentrations after single or repeated administration to ICR mice on days (a) 0 (b) 7 and (c) 21. Cisplatin (CIS; 7.5 mg/kg, i.p.) and docetaxel (DOC; 12.5 mg/kg i.p.) were administered separately, or every 7 days simultaneously (DOC/CIS; n = 4–9) or sequentially 12 h apart (DOC–CIS; n = 4–7 and CIS–DOC; n = 5–7). Values are means ± SD.

Renal toxicity depends on the cisplatin concentration.[17,18] In the present study, AUC_{0-12h} of cisplatin in plasma was higher by 1.3–1.4-fold in the docetaxel/cisplatin group than in the cisplatin–docetaxel and docetaxel–cisplatin groups after a single administration (data not shown). After a single administration, renal cisplatin concentration was higher in the docetaxel/cisplatin group than in the cisplatin–docetaxel and docetaxel–cisplatin groups. Cisplatin-induced nephrotoxicity becomes severe when the kidney cisplatin level is high.[19] Thus, the increase in cisplatin concentrations in plasma and kidney may have inhibited renal function in the docetaxel/cisplatin group.

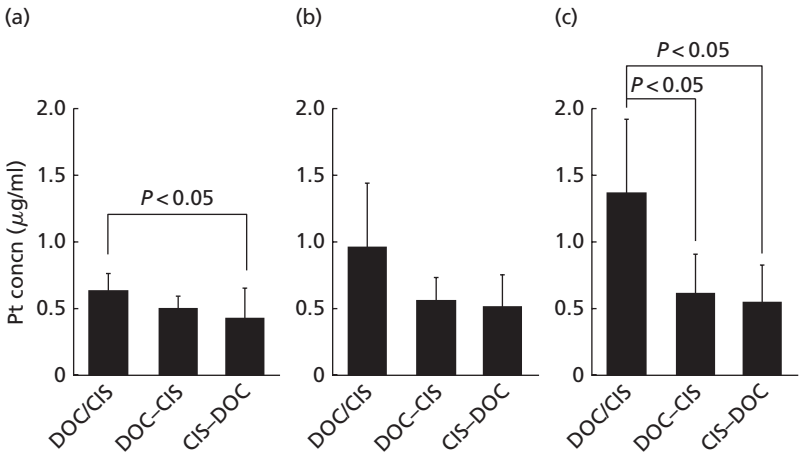

Figure 5 Influence of dosing schedule on plasma cisplatin concentrations after single or repeated administration to ICR mice on days (a) 0 (b) 7 and (c) 21. Cisplatin (CIS; 7.5 mg/kg i.p.) and docetaxel (DOC; 12.5 mg/kg i.p.) were administered once or every 7 days simultaneously (DOC/CIS; n = 6–9) or intermittently (DOC–CIS; n = 6–8 and CIS–DOC; n = 6–8). Values are means ± SD.

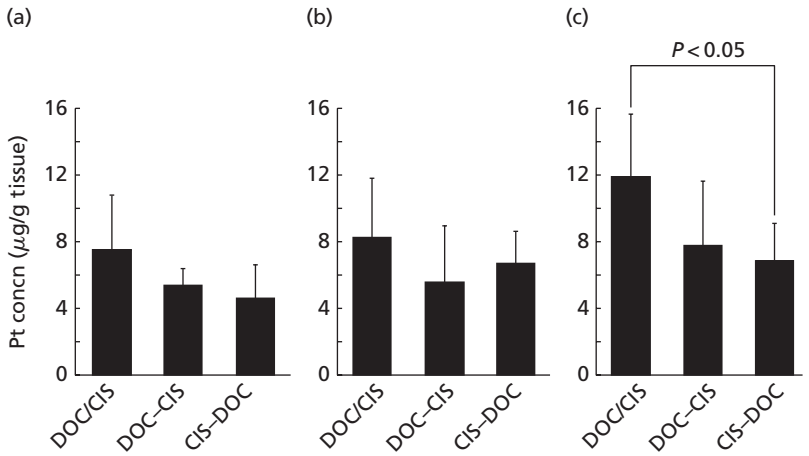

Figure 6 Influence of dosing schedule on cisplatin concentrations in the kidney 4 h after single or repeated cisplatin administration to ICR mice on days (a) 0 (b) 7 and (c) 21. Cisplatin (CIS; 7.5 mg/kg i.p.) and docetaxel (DOC; 12.5 mg/kg i.p.) were administered every 7 days simultaneously (DOC/CIS; n = 8) or sequentially, 12 h apart (DOC–CIS; n = 8 and CIS–DOC; n = 8). Values are means ± SD.

The main route of excretion of cisplatin is via the urine, with 40–50% being excreted within 4 h.[20] In this study, the simultaneous dosing schedule resulted in higher levels in plasma and kidney than did the sequential regimens. Thus, a drug–drug interaction that affects the renal excretion of cisplatin might occur when docetaxel and cisplatin are administered together. Cisplatin is filtered by the glomerulus and is secreted from the renal tubule via drug transporters.[21,22] The proximal tubule expresses drug transporters such as P-glycoprotein (P-gp) and multidrug resistance associated protein-2 (MRP-2);[23,24] docetaxel is a substrate for both P-gp and MRP-2.[25–27] Although the exact mechanisms underlying the secretion of cisplatin via the renal tubule are not fully understood, it has been reported that cisplatin is not a substrate of P-gp,[28] but is a substrate of MRP-2.[29] The increase in cisplatin concentrations in the plasma and kidney in the docetaxel/cisplatin group suggests competitive inhibition between cisplatin and docetaxel in excretion via the MRP-2.

When cisplatin and docetaxel were administered repeatedly, cisplatin accumulated markedly in the plasma and kidney in the docetaxel/cisplatin group compared with the cisplatin–docetaxel and docetaxel–cisplatin groups. Impaired renal function reduces cisplatin excretion, and this is aggravated when cisplatin is administered repeatedly.[30,31] Plasma and renal levels of cisplatin were higher in the docetaxel/cisplatin group than in the cisplatin–docetaxel and docetaxel–cisplatin groups. The exposure to high cisplatin concentrations may trigger more severe nephrotoxicity. The nephrotoxicity caused by a single administration in the docetaxel/cisplatin group results in decreased renal excretion of cisplatin. Repeated injection of cisplatin resulted in accumulation of the drug in the plasma and kidneys, which could aggravate the renal dysfunction, explaining the high

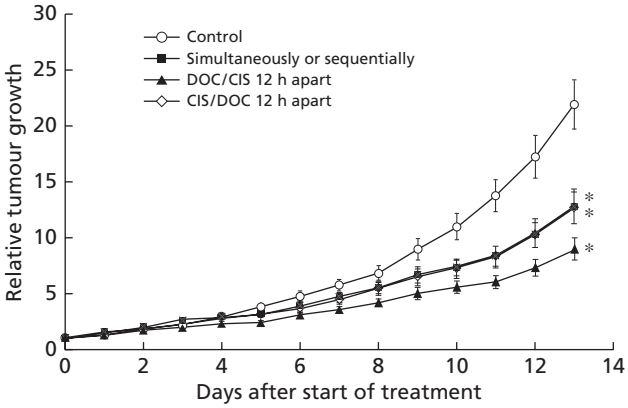

Figure 7 Influence of dosing schedule on tumour growth after the combined administration of cisplatin and docetaxel in C57BL/6N mice inoculated with Lewis lung carcinoma cells. Cisplatin (7.5 mg/kg i.p.) and docetaxel (12.5 mg/kg i.p.) were administered every 7 days simultaneously (docetaxel/cisplatin, $n = 14$) or sequentially, 12 h apart (docetaxel–cisplatin, $n = 14$; and cisplatin–docetaxel, $n = 14$). The control group was not treated ($n = 13$). Values are means ± SE. $^*P < 0.05$ vs control group.

mortality in the docetaxel/cisplatin group compared with the cisplatin–docetaxel and docetaxel–cisplatin groups.

Although there were no significant differences in plasma docetaxel concentrations among the treatment groups after a single drug administration, the docetaxel level was higher in the docetaxel/cisplatin group than in the cisplatin–docetaxel and docetaxel–cisplatin groups with repeated administration. Docetaxel is metabolised in the liver, mainly by hepatic cytochrome P450 (CYP)3A4.[32,33] Although no clear mechanism is known, reduction in CYP activity and protein are associated with cisplatin-induced renal failure.[34,35] In this study, severe renal failure was seen in the docetaxel/cisplatin group, in which the plasma docetaxel concentration increased. The increase in plasma docetaxel level in the docetaxel/cisplatin group may have resulted from impaired renal function, facilitated by reduction of activity and protein expression of CYP3A.

On day 14, rates for inhibition of tumour growth were 42.3% in the docetaxel/cisplatin group, 41.8% in the cisplatin–docetaxel and 59.1% in the docetaxel–cisplatin group; antitumour effect was greatest in the docetaxel–cisplatin group.

It has been reported that the antitumour effect of co-administered cisplatin and docetaxel in human cancer cells *in vitro* is highly dependent on the dosing schedule: inhibition of tumour cell growth was higher when cells were exposed to cisplatin after docetaxel compared with cisplatin and docetaxel simultaneously.[36,37] The results of this in-vitro study corresponded to the results of our in-vivo study. The enhanced cytotoxicity of cisplatin when administered after docetaxel pre-treatment was attributed to accumulation of intracellular Pt–glutathione complexes, as docetaxel appears to suppress the MRP-1 up-regulation induced by cisplatin exposure,[37] and pre-treatment with cisplatin significantly blocked the subsequent docetaxel-induced apoptosis.[36] The antagonistic effect between docetaxel and cisplatin and the intracellular cisplatin pharmacokinetics in tumour rather than plasma drug concentrations are likely to have contributed to the difference in antitumour effect between the groups.

Conclusions

The findings of the present study reveal that the docetaxel–cisplatin regimen, in which cisplatin was administered 12 h after docetaxel injection, not only inhibited tumour growth to the greatest extent among the dosing groups but also significantly reduced the toxic death and nephrotoxicity compared with the cisplatin/docetaxel regimen commonly used in clinical practice. The difference in nephrotoxicity may be caused by the pharmacokinetics of cisplatin and docetaxel. The 12 h dosing interval used in this study may not be the optimal dosing schedule for docetaxel and cisplatin in the clinic. Nevertheless, this study demonstrates that sequential dosing may be preferable to simultaneous dosing. Choosing a dosing schedule based on evidence from basic and clinical studies may improve the safety and efficacy of chemotherapy with combinations of cisplatin and docetaxel.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This study was supported by a Grant-in-Aid for Scientific Research on Priority Areas (H To, 18014021, 20014019) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. This project was partially supported by the research Foundation for Pharmaceutical Sciences (H To).

Acknowledgement

We are indebted to Nippon Kayaku Co. Ltd (Tokyo, Japan) for supplying the cisplatin used in this study.

References

1. Fossella F *et al.* Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003; 21: 3016–3024.
2. Kubota K *et al.* Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. *J Clin Oncol* 2004; 22: 254–261.
3. Le Chevalier T *et al.* Docetaxel (Taxotere) plus cisplatin: an active and well-tolerated combination in patients with advanced non-small cell lung cancer. *Eur J Cancer* 1998; 34: 2032–2036.
4. Zalcberg J *et al.* Phase II study of docetaxel and cisplatin in advanced non-small-cell lung cancer. *J Clin Oncol* 1998; 16: 1948–1953.
5. Krakoff IH. Nephrotoxicity of cis-dichlorodiammineplatinum (II). *Cancer Treat Rep* 1979; 63: 1523–1525.

6. Offerman JJ *et al.* Acute effects of cis-diamminedichloroplatinum (CDDP) on renal function. *Cancer Chemother Pharmacol* 1984; 12: 36–38.
7. Bardos G *et al.* BGP-15, a hydroximic acid derivative, protects against cisplatin- or taxol-induced peripheral neuropathy in rats. *Toxicol Appl Pharmacol* 2003; 190: 9–16.
8. Verschraagen M *et al.* Possible (enzymatic) routes and biological sites for metabolic reduction of BNP7787, a new protector against cisplatin-induced side-effects. *Biochem Pharmacol* 2004; 68: 493–502.
9. Ajith TA *et al.* Ascorbic acid and alpha-tocopherol protect anticancer drug cisplatin induced nephrotoxicity in mice: a comparative study. *Clin Chim Acta* 2007; 375: 82–86.
10. To H *et al.* Influence of dosing schedule on toxicity and antitumor effects of a combination of adriamycin and docetaxel in mice. *Clin Cancer Res* 2004; 10: 762–769.
11. Tabuchi M *et al.* Therapeutic index by combination of adriamycin and docetaxel depends on dosing time in mice. *Cancer Res* 2005; 65: 8448–8454.
12. Sakaguchi H *et al.* Pre-administration of docetaxel protects against adriamycin-induced cardiotoxicity. *Breast Cancer Res Treat* 2008; 109: 443–450.
13. Kuroki M *et al. In vivo* comparative therapeutic study of optimal administration of 5-fluorouracil and cisplatin using a newly established HST-1 human squamous-carcinoma cell line. *Cancer Chemother Pharmacol* 1992; 29: 273–276.
14. Cao S, Rustum YM. Synergistic antitumor activity of irinotecan in combination with 5-fluorouracil in rats bearing advanced colorectal cancer: role of drug sequence and dose. *Cancer Res* 2000; 60: 3717–3721.
15. Kelly KJ *et al.* Protection from toxicant-mediated renal injury in the rat with anti-CD54 antibody. *Kidney Int* 1999; 56: 922–931.
16. Townsend DM, Hanigan MH. Inhibition of gamma-glutamyl transpeptidase or cysteine S-conjugate beta-lyase activity blocks the nephrotoxicity of cisplatin in mice. *J Pharmacol Exp Ther* 2002; 300: 142–148.
17. Goldstein RS *et al.* cis-Dichlorodiammineplatinum nephrotoxicity: time course and dose response of renal functional impairment. *Toxicol Appl Pharmacol* 1981; 60: 163–175.
18. Mizushima Y *et al.* Studies on nephrotoxicity following a single and repeated administration of cis-diamminedichloroplatinum (CDDP) in rats. *Tohoku J Exp Med* 1987; 151: 129–135.
19. Kawai Y *et al.* Relationship between cisplatin or nedaplatin-induced nephrotoxicity and renal accumulation. *Biol. Pharm. Bull*. 2005; 28: 1385–1388.
20. Siddik ZH *et al.* The comparative pharmacokinetics of carboplatin and cisplatin in mice and rats. *Biochem Pharmacol* 1987; 36: 1925–1932.
21. Caterson R *et al.* Mechanisms of renal excretion of cisdichloro diamine platinum. *Res Commun Chem Pathol Pharmacol* 1983; 41: 255–264.
22. Jacobs C *et al.* Inhibition of cis-diamminedichloroplatinum secretion by the human kidney with probenecid. *Cancer Res* 1984; 44: 3632–3635.
23. Tsuruoka S *et al.* P-glycoprotein-mediated drug secretion in mouse proximal tubule perfused *in vitro*. *J Am Soc Nephrol* 2001; 12: 177–181.
24. Robertson EE, Rankin GO. Human renal organic anion transporters: characteristics and contributions to drug and drug metabolite excretion. *Pharmacol Ther* 2006; 109: 399–412.
25. Shirakawa K *et al.* Interaction of docetaxel ("Taxotere") with human P-glycoprotein. *Jpn J Cancer Res* 1999; 90: 1380–1386.
26. van Zuylen L *et al.* Role of intestinal P-glycoprotein in the plasma and fecal disposition of docetaxel in humans. *Clin Cancer Res* 2000; 6: 2598–2603.
27. Huisman MT *et al.* MRP2 (ABCC2) transports taxanes and confers paclitaxel resistance and both processes are stimulated by probenecid. *Int J Cancer* 2005; 116: 824–829.
28. Hamaguchi K *et al.* Cross-resistance to diverse drugs is associated with primary cisplatin resistance in ovarian cancer cell lines. *Cancer Res* 1993; 53: 5225–5232.
29. Cui Y *et al.* Drug resistance and ATP-dependent conjugate transport mediated by the apical multidrug resistance protein, MRP2, permanently expressed in human and canine cells. *Mol Pharmacol* 1999; 55: 929–937.
30. Litterst CL, Schweitzer VG. Increased tissue deposition and decreased excretion of platinum following administration of cisplatin to cisplatin-pretreated animals. *Cancer Chemother Pharmacol* 1984; 12: 46–49.
31. Reece PA *et al.* Reduced ability to clear ultrafilterable platinum with repeated courses of cisplatin. *J Clin Oncol* 1986; 4: 1392–1398.
32. Royer I *et al.* Metabolism of docetaxel by human cytochromes P450: interactions with paclitaxel and other antineoplastic drugs. *Cancer Res* 1996; 56: 58–65.
33. Shou M *et al.* Role of human cytochrome P450 3A4 and 3A5 in the metabolism of taxotere and its derivatives: enzyme specificity, interindividual distribution and metabolic contribution in human liver. *Pharmacogenetics* 1998; 8: 391–401.
34. Okabe H *et al.* The hepatic and intestinal metabolic activities of P450 in rats with surgery- and drug-induced renal dysfunction. *Pharm Res* 2003; 20: 1591–1594.
35. Masubuchi Y *et al.* Down-regulation of hepatic cytochrome P450 enzymes associated with cisplatin-induced acute renal failure in male rats. *Arch Toxicol* 2006; 80: 347–353.
36. Wang H. Combined effect of docetaxel and cisplatin for non-small cell lung cancer cell lines *in vitro*. *Nagoya J Med Sci* 2000; 63: 129–137.
37. Maeda S *et al.* Docetaxel enhances the cytotoxicity of cisplatin to gastric cancer cells by modification of intracellular platinum metabolism. *Cancer Sci* 2004; 95: 679–684.