Population pharmacokinetics of docetaxel in patients with hepatic dysfunction treated in an oncology practice

Hironobu Minami,[1,2,4] Kenji Kawada,[2] Yasutsuna Sasaki,[2] Makoto Tahara,[2] Tadahiko Igarashi,[2] Kuniaki Itoh,[2] Hirofumi Fujii,[2] Toshiaki Saeki,[2] Kazuhiro Ozawa[3] and Hitoshi Sato[3]

[1]Medical Oncology, Department of Medicine, Kobe University Hospital and Graduate School of Medicine, Hyogo 650-0017; [2]Division of Oncology and Hematology, National Cancer Center Hospital East, Chiba 277-8577; [3]Department of Clinical and Molecular Pharmacokinetics and Pharmacodynamics, School of Pharmaceutical Sciences, Showa University, Tokyo 142-8555, Japan

(Received April 25, 2008/Revised August 22, 2008/Accepted September 1, 2008/Online publication October 31, 2008)

To investigate the relationship between the degree of liver dysfunction and the pharmacokinetics of docetaxel, a population pharmacokinetic model was developed in an oncology practice without excluding patients with moderate to severe liver dysfunction. Two hundred patients were treated with docetaxel as a single agent or in combination chemotherapy. The plasma concentration–time course data were analyzed using a three-compartment open model with zero-order administration and first-order elimination on the NONMEM program. Sixty-one had elevated transaminase levels, and alkaline phosphatase was elevated in 40. Body surface area, albumin, α_1-acid glycoprotein, and liver function were found to be significant covariates for the systemic clearance of docetaxel. Compared to patients with normal or minimal impairment of liver function, patients with grade 2 and 3 elevations of transaminases at baseline in conjunction with elevation of alkaline phosphatase had 22 and 38% lower clearances, respectively. Goodness-of-fit plots indicated that the model was fitted well with the observed data, and the bootstrap method guaranteed robustness of the model. We developed a population pharmacokinetic model for docetaxel, which can be used in the setting of an oncology practice. Based on the model, dose reduction by approximately 20 and 40% should be considered for patients with grade 2 and 3 elevations of transaminases at baseline in conjunction with elevation of alkaline phosphatase, respectively. (*Cancer Sci* 2009; 100: 144–149)

Anticancer drugs have a narrow therapeutic window, and interpatient variabilities in pharmacokinetics and pharmacodynamics may results in serious toxicities.[1] Elucidating the factors causing these interpatient variabilities is helpful for avoiding serious toxicities and augmenting antitumor activity. Population pharmacokinetics represent a means to investigate the effect of patients' variables on the pharmacokinetics of drugs.[2–4] In this approach, pharmacokinetics are analyzed in many patients with different backgrounds as a population, and the effect of these backgrounds on the pharmacokinetics are investigated. Pharmacokinetic information on patients with small numbers of drug concentration data can also be analyzed by population pharmacokinetic methodology.[2–5] Thus, it is a useful tool for investigating pharmacokinetics of drugs in a population including elderly patients or patients with organ dysfunctions.

Docetaxel has been used widely to treat breast, non-small-cell lung, ovarian, head and neck, gastric, esophageal, and prostate cancers.[6–15] The drug is eliminated from the body mainly by hepatic metabolism. Population pharmacokinetic models of docetaxel have been developed using data obtained from patients treated in clinical trials prior to its drug registration,[16–18] where body surface area, albumin, age, α_1-acid glycoprotein, and liver function were found to be significant covariates for the systemic clearance of docetaxel. In clinical studies for the development of anticancer drugs, unfit patients including those with moderate to severe liver dysfunction or poor performance status are commonly excluded, and information on pharmacokinetics and pharmacodynamics for such patients is therefore lacking.

Therefore, in the present study, we developed a population pharmacokinetic model of docetaxel in cancer patients treated in our oncology practice, including unfit patients who would have been excluded from the past clinical studies during drug development, and investigated the pharmacokinetic alterations of docetaxel in relation to the extent of liver function impairment. In the previous population pharmacokinetic study, which was carried out as part of the clinical trial program for drug approval, only 3% of patients had pharmacokinetically relevant liver dysfunction compared with 9% in our study.[16]

Materials and Methods

Patient selection. Patients with different cancers receiving docetaxel as a single agent or in combination chemotherapy in medical practice were eligible for this population pharmacokinetic study. Other eligibility criteria included being 20 years old or older, performance status of 3 or better, white blood cell count ≥3000/mL, and platelet count ≥75 000/mL. The dose and schedule of docetaxel were set according to the approved usage in Japan, that is, intravenous 60-min infusion at a dose of 60 mg/m^2 every 3 weeks. However, the dose and schedule were modified in combination chemotherapy or based on the extent of liver impairment or performance status in each patient at the discretion of attending physicians. All patients gave written informed consent, and this study was approved by the Institutional Review Board at the National Cancer Center, Japan.

Treatment and follow up. For the measurement of docetaxel concentrations in plasma, heparinized blood was collected. Blood sampling at the end of docetaxel infusion, and 0.17, 1, 5, 10, and 24 h thereafter was recommended, but this was allowed to be rather flexible depending on clinical situations. However, exact infusion time and sampling times were recorded accurately. Plasma concentrations of docetaxel were determined by a high-performance liquid chromatographic method as reported previously.[19]

Population pharmacokinetic analysis. Population pharmacokinetic analyses were carried out using a non-linear mixed-effect modeling program, NONMEM (version V, level 1.1; ICON DEVELOPMENT Solutions, Ellicott City, MD, USA). NONMEM was running with a Compaq Visual FORTRAN 6.6 compiler

*To whom correspondence should be addressed.
E-mail: hminami@med.kobe-u.ac.jp

doi: 10.1111/j.1349-7006.2009.00992.x

(Hewlett-Packard, Palo Alto, CA, USA) on a Pentium 4 central processing unit, under the Windows XP operating system (Microsoft Corporation, Redmond, WA, USA). After one- and two-compartment models were tested, a three-compartment open model with zero-order administration and first-order elimination (ADVAN 11 and TRANS 4) was selected to describe the plasma concentration–time course for docetaxel in the entire population based on goodness of fit to the data. The pharmacokinetic model was parameterized in terms of clearance (CL), the volume of distribution of the central compartment (V_1) as well as those of two peripheral compartments (V_2 and V_3), and intercompartment clearances (Q_2 and Q_3). Assuming a log-normal distribution for interindividual variability in pharmacokinetic parameters, the interindividual variability was modeled as (e.g. for clearance):

$$CL_j = \widehat{CL} \cdot \exp(\eta_{jCL}),$$

where CL_j and $\widehat{CL}$ are the estimated values in an individual j and the population mean for clearance, respectively, and η_{jCL} is the individual random perturbation with a mean of zero and a variance ω^2. Intraindividual residual variability was also described by a log-normal distribution model. The first-order conditional estimation method was used to estimate the pharmacokinetic parameters.

Relationships between covariates and pharmacodynamic parameters. The following covariates were tested to improve the population pharmacokinetic model: age, sex, body surface area, performance status, albumin, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatinine, and coadministered anticancer agents. Forward selection and backward elimination were used to select covariates to be included in the model. Statistical discrimination between hierarchial models was based on difference in objective function (Obj) in NONMEM analyses, equal to minus twice the log likelihood of the data. Covariates were inserted sequentially into the basic model by forward selection. During this process, $P < 0.001$ was considered significant, corresponding to a decrease in Obj of 10.83 and 13.82 for degrees of freedom of 1 and 2, respectively. Continuous variables were normalized by their population median and were expressed by multiplicative models. Multiplicative models were used to enhance convergence and were coded as:

$$P = \beta_1 \cdot COV^{\beta_2}$$

where P is the individual's estimate of the parameters, β_1 represents the typical value of the parameter, β_2 represents the effect of the covariate, and COV is the ratio of the individual's covariate value to the median value. For convenience in clinical application, hepatic function was categorized according to grade by the National Cancer Center Institute Common Toxicity Criteria. Each liver function test (e.g. AST, ALT, ALP, bilirubin) and their combinations (e.g. the maximum grade of AST and ALT) were tested as covariates. After all significant variables were included in the model, each covariate was removed in a stepwise backward elimination procedure to determine whether it was significant in the final model.

Bootstrap validation. The accuracy and robustness of the final model were assessed by using a bootstrap method.[20–22] A bootstrap sample was generated by repeated random sampling from the original data set, and the size of bootstrap sample was the same as the original sample size. Two hundred bootstrap samples were reconstructed, and the final model is fitted repeatedly to the 200 bootstrap samples. The mean parameter estimates obtained from bootstrap replications that were calculated normally were compared with those obtained from the original data set.

Table 1. Demographics of patients

Demographic		No. patients
Age (years)		
Median	57	
Range	21–86	
Sex		
Female		114
Male		86
Performance status		
0		46
1		130
2		17
3		7
Combination chemotherapy		
Cisplatin		66
Doxorubicin		6
Irinotecan		31
Cancer		
Breast cancer		79
Non-small cell lung cancer		68
Head and neck cancer		31
Others		22
Dose of docetaxel (mg/m²)		
–25		30
35		59
45		9
55		16
60		86
Infusion time (h)		
0.5		52
1.0		128
1.5		20
Body surface area (mg/m²)		
Median	1.53	
Range	1.17–1.99	
Liver function		
HEP1		183
HEP2		10
HEP3		7

HEP1, normal liver function (normal alkaline phosphatase [ALP] or <grade 2 elevation of aspartate aminotransferase [AST] or alanine aminotransferase [ALT]); HEP2, mild liver dysfunction (increased ALP in combination with grade 2 elevation of AST or ALT); HEP3, moderate liver dysfunction (increased ALP in combination with grade 3 or greater elevation of AST or ALT).

Results

We analyzed pharmacokinetic data from 200 cancer patients with different backgrounds, including 18 patients older than 75 years and seven patients with a performance status of 3 (Table 1). Docetaxel was given in combination chemotherapy with cisplatin, doxorubicin, or irinotecan in 103 patients, with the dose ranging from 15 to 60 mg/m². Hypoalbuminemia was observed in 137 patients at baseline, and AST or ALT levels were elevated in 61 patients (Table 2), including 17 with grade 2 or greater elevation of AST or ALT in combination with elevated ALP levels. Serum bilirubin was increased in five patients but was associated with elevated transaminase levels in only two patients.

The actual number of plasma concentration data per patient ranged from two to nine with a median of six. Concentration–time curves were best described by a three-compartment linear model (Fig. 1). First, population pharmacokinetic parameters were computed using a simple structural model without any covariates, and the influence of covariates on the clearance of

Table 2. Blood chemistry of patients

Liver function	Grade			
	0	1	2	3
Albumin				
Concentration (g/dL)	≥4.0	3.0–3.9	2.0–2.9	≤1.9
No. patients	63	126	10	1
Total bilirubin				
Concentration (mg/dL)	≤1.2	1.3–1.5	1.6–3.6	3.7–12
No. patients	195	3	1	1
Aspartate aminotransferase				
Concentration (IU/L)	≤33	34–82	83–165	166–660
No. patients	157	27	10	6
Alanine aminotransferase				
Concentration (IU/L)	≤27	28–67	68–135	136–540
No. patients	145	43	6	6
Alkaline phosphatase				
Concentration (IU/L)	≤359	360–897	898–1795	1796–7140
No. patients	160	26	11	3
α_1-Acid glycoprotein				
Concentration (mg/dL)	≤93[†]	94–232[‡]	233–465[§]	
No. patients	90	107	3	

[†]≤Upper limit of normal range (ULN); [‡]>ULN and ≤2.5 × ULN; [§]>2.5 × ULN and ≤5 × ULN.

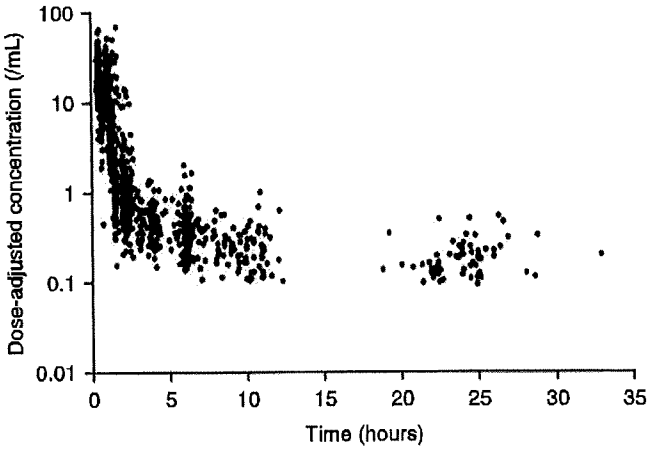


Fig. 1. Observed plasma concentration of docetaxel. Concentrations were normalized by the actual dose of docetaxel in each patient.

docetaxel was investigated. Body surface area, albumin, liver function index, and α_1-acid glycoprotein improved the model when included as covariates (Table 3). Among the different indices of liver function investigated, the combination of ALP and the maximum grade of AST or ALT improved the model to the highest extent. In this model, patients were classified into three groups: seven patients with elevated ALP (i.e. grade ≥ 1) in combination with grade 3 or greater elevation of AST or ALT (HEP3), 10 with elevated ALP in combination with grade 2 elevation of AST or ALT (HEP2), and 183 with normal or minimum liver dysfunction (HEP1).

The predicted values obtained by Bayesian estimation are plotted versus the observed values in Figure 2a. Weighted residual plots for the population pharmacokinetic model are shown in Figure 2b. The values were generally distributed around zero and were relatively symmetrical. No obvious bias pattern was apparent in the plot of the predicted concentration versus the weighted residual. Pharmacokinetic parameters in the population pharmacokinetic model are summarized in Table 4. Among the 200 bootstrap samples, 153 samples were converged. All structural parameters (θ_i) and variance parameters (ω, σ) were within 19.5% of the bootstrapped mean out of the 153 samples (Table 4). Systemic clearance of docetaxel was positively correlated with body surface area and albumin, and negatively correlated with α_1-acid glycoprotein. In patients with mild (HEP2) and moderate (HEP3) liver dysfunction, clearance was reduced by 22 and 38%, respectively. The difference in the reduction of systemic clearance between each category of liver dysfunction was highly significant ($P < 0.001$). These reductions were apparent when the systemic clearance of docetaxel for individuals was calculated by Bayesian estimation and compared in relation to liver function (Fig. 3).

Discussion

A population pharmacokinetic approach allows us to analyze data with small numbers of samples per patient, and can be used to investigate pharmacokinetics in unfit patients treated in oncology practice where full pharmacokinetic sampling may be difficult. Therefore, we used the methodology of population pharmacokinetics in Japanese patients treated in oncology practice, in order to investigate the influence of patients' various backgrounds on the pharmacokinetics of docetaxel.

Goodness-of-fit plots (Fig. 2) indicated that the present population pharmacokinetic model was fitted well with the observed data. Table 4 indicates that a convergence ratio on bootstrap data was so high that the robustness of this model was sufficiently guaranteed. The differences between θ_i of the final model estimates and those of the bootstrap means were relatively small. Therefore, the parameter estimates on bootstrap samples corresponded well with the original data.

Table 3. Model building

Model	Covariates	Objective function(Obj)	Difference in objective function	*P*
1	None	−5072		
2	BSA	−5303	−230	<0.0001*
3	BSA, ALB	−5538	−235	<0.0001*
4	BSA, ALB, HEP	−5554	−16	<0.0001*
5	BSA, ALB, HEP, AGP	−5574	−20	<0.0001*
6	BSA, ALB, AGP	−5556	+18	<0.0001**
7	BSA, HEP, AGP	−5469	+105	<0.0001**
8	BSA, ALB, HEP	−5543	+30	<0.0001**

*Compared to the previous model. **Compared to Model 5 (final model). AGP, α_1-acid glycoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; HEP, normal, mildly (increased ALP in combination with grade 2 elevation of AST or ALT) or moderately elevated liver function tests (increased ALP in combination with grade 3 or greater elevation of AST or ALT).

doi: 10.1111/j.1349-7006.2009.00992.x

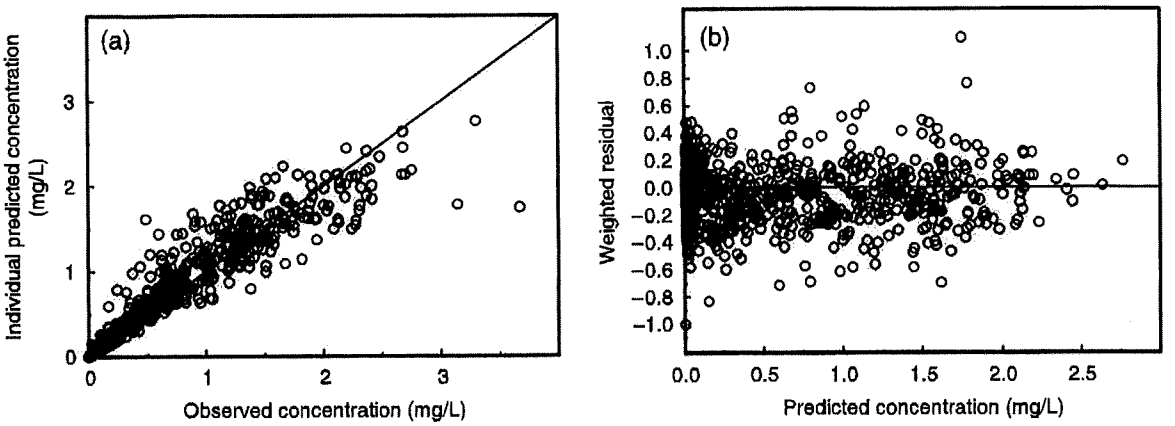


Fig. 2. (a) Observed docetaxel concentration versus predicted docetaxel concentration from a Bayesian post hoc analysis of the model. The solid line represents the unit line. (b) Weighted residuals versus predicted concentration. The horizontal line represents the zero level.

Table 4. Estimation and precision of parameters in population pharmacokinetic model of docetaxel and bootstrap validation

Parameter	θ	Estimated parameters (precision†)		Difference§
		Original analysis	Bootstrap validation‡	
Clearance (L/h)	θ_1	29.3 (4)	28.3 (9)	3.31
Body surface area	θ_2	1.11 (26)	1.15 (29)	−3.87
Albumin	θ_3	2.00 (26)	1.94 (26)	2.80
α_1-Acid glycoprotein	θ_4	0.251 (29)	0.260 (35)	−4.20
LIV	θ_5	0.776 (14)	0.759 (21)	2.18
	θ_6	0.623 (24)	0.616 (31)	1.17
V_1 (L)	θ_7	7.75 (5)	7.63 (4)	1.57
Q_2 (L/h)	θ_8	5.46 (9)	5.67 (14)	−3.81
V_2 (L)	θ_9	8.69 (14)	9.55 (26)	−9.91
Q_3 (L/h)	θ_{10}	19.0 (10)	19.7 (17)	−3.52
V_3 (L)	θ_{11}	660 (14)	789 (41)	−19.5
Interindividual variability (%)				
ω_{CL}		31 (23)	31 (12)	−0.65
ω_{V1}		19 (38)	18 (27)	2.69
ω_{Q3}		31 (22)	32 (9)	−3.02
ω_{V3}		38 (35)	37 (35)	0.566
Intraindividual variability (%)				
σ		29 (19)	29 (11)	1.46

†Expressed as Coefficient of variation. ‡Calculated from 200 bootstrap replicates (153 convergence). §(Original value − bootstrap value)/original value × 100 (%). The equation used to estimate the population parameters was Clearance = θ_1 × (body surface area/1.53)$^{\theta_2}$ × (albumin/3.7)$^{\theta_3}$ × (97/α_1-acid glycoprotein)$^{\theta_4}$ × LIV × EXP(η_1), where LIV = 1 for normal ALP or <grade 2 elevation of AST or ALT, LIV = θ_5 for increased ALP in combination with grade 2 elevation of AST or ALT, and θ_6 for increased ALP in combination with ≥grade 3 elevation of AST or ALT.

The present analysis indicated that the systemic clearance of the drug was significantly correlated to body surface area, albumin, α_1-acid glycoprotein, and liver function. Bruno *et al.* previously developed a population pharmacokinetic model for docetaxel in patients treated in clinical studies carried out for drug registration, and found the same factors to be significant determinants of clearance.[16] Although age was incorporated as a covariate for clearance in their model, it was not applied to our study. The estimated coefficient of age in their model was small, and a difference of 20 years in age would yield less than a 10% difference in clearance of the drug. Furthermore, in two independent pharmacokinetic and pharmacodynamic studies of docetaxel comparing elderly and non-elderly patients, pharmacokinetics were found not to be different between the two groups, although the same exposure to docetaxel resulted in more toxicities in elderly patients.[23,24]

In previous population pharmacokinetic studies of docetaxel,[16–18] liver function was a significant covariate for clearance. A 33% reduction in clearance was observed for patients with AST or ALT > 60 IU together with ALP > 300 IU in a population pharmacokinetic model developed for patients in the USA and European countries,[16] whereas patients with AST or ALT > 60 IU/L had 21% lower clearance in a model for Japanese patients.[18] Liver function was incorporated as a binary covariate into these models because patients with clinically significant impairment of liver function had been excluded from these studies carried out for drug approval. In contrast, patients with significant liver dysfunction were included in our study, although the number of patients with liver dysfunction was small compared to those with normal liver function, and reductions in clearance could be estimated in relation to the extent of liver function impairment. Thus, 22 and 38% reductions were observed for mild and moderate liver dysfunction, respectively (Table 4). Dividing patients into three groups based on their liver function yielded better results than classifying them into two groups (data not shown), and the difference in the reduction of systemic

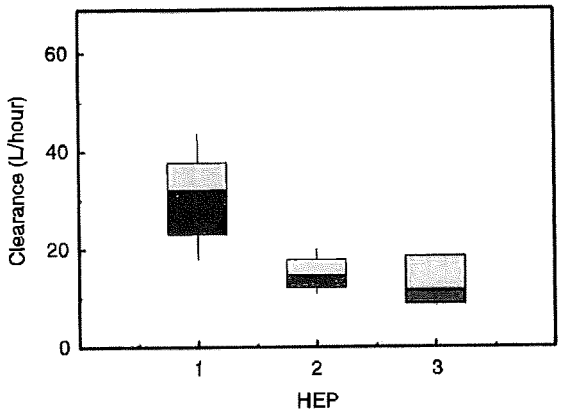


Fig. 3. Box plot of estimated systemic clearance of docetaxel according to hepatic function calculated by Bayesian estimation. The top, middle, and bottom lines of each box correspond to the 75% (top quartile), 50% (median), and 25% (bottom quartile) values. The whiskers show the range values that fall between 10 and 90%. 1, 2, and 3 HEP denote normal ($n = 183$), mildly (increased alkaline phosphatase [ALP] in combination with grade 2 elevation of aspartate aminotransferase [AST] or alanine aminotransferase [ALT], $n = 10$), and moderately elevated liver function tests (increased ALP in combination with grade 3 or greater elevation of AST or ALT, $n = 7$), respectively.

clearance of docetaxel between patients with mild and moderate liver dysfunction was highly significant.

Our population pharmacokinetic study was not designed to investigate pharmacodynamics; patients treated with docetaxel in various combination regimens were included and toxicities were not monitored in a uniform way. Therefore, relationships between liver function and toxicities could not be investigated. However, based on the alterations of observed docetaxel clearance, dose reductions by approximately 20 and 40% would be a reasonable strategy for patients with grade 2 and 3 elevations of AST or ALT in combination with elevated ALP, although variability in concentrations of docetaxel might be observed even with this dose adjustment because liver function is not the only source of pharmacokinetic variability. Furthermore, this recommendation requires further validation in a prospective study.

Population pharmacokinetics of many anticancer agents are currently being investigated as a part of clinical development;[25–31] however, unfit patients, including those with organ dysfunction or poor performance status, are commonly excluded from clinical trials, resulting in a paucity of pharmacokinetic information for these groups. After drugs are approved, however, these patients are treated in medical practice, and dose reduction may be required at the discretion of attending physicians. It is therefore important to collect actual pharmacokinetic information in this context.

In conclusion, we developed a population pharmacokinetic model for docetaxel that can be used in the setting of an oncology practice. It was found that body surface area, albumin, α_1-acid glycoprotein, and liver function are significant covariates for the systemic clearance of docetaxel. According to the reductions of docetaxel clearance in patients with liver dysfunction predicted by our model, dose reduction by approximately 20 and 40% should be considered for patients with grade 2 and 3 elevations of transaminases at baseline in conjunction with elevation of alkaline phosphatase, respectively.

Acknowledgments

The present study was supported in part by a Grant-in-Aid for Cancer Research (17-8) from the Ministry of Health, Labor, and Welfare of Japan and by Kobayashi Institute for Innovative Cancer Chemotherapy.

References

1 Ratain MJ, Schilsky RL, Conley BA, Egorin MJ. Pharmacodynamics in cancer therapy. *J Clin Oncol* 1990; **8**: 1739–53.
2 Minto C, Schnider T. Expanding clinical applications of population pharmacodynamic modelling. *Br J Clin Pharmacol* 1998; **46**: 321–33.
3 Sun H, Fadiran E, Jones C *et al.* Population pharmacokinetics. A regulatory perspective. *Clin Pharmacokinet* 1999; **37**: 41–58.
4 Samara E, Granneman R. Role of population pharmacokinetics in drug development: a pharmaceutical industry perspective. *Clin Pharmacokinet* 1997; **32**: 294–312.
5 Ludden T. Population pharmacokinetics. *J Clin Pharmacol* 1988; **28**: 1059–63.
6 Jones SE, Savin MA, Holmes FA *et al.* Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol* 2006; **24**: 5381–7.
7 Bear HD, Anderson S, Brown A *et al.* The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project protocol B-27. *J Clin Oncol* 2003; **21**: 4165–74.
8 Georgoulias V, Ardavanis A, Tsiafaki X *et al.* Vinorelbine plus cisplatin versus docetaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III randomized trial. *J Clin Oncol* 2005; **23**: 2937–45.
9 Georgoulias V, Ardavanis A, Agelidou A *et al.* Docetaxel versus docetaxel plus cisplatin as front-line treatment of patients with advanced non small-cell lung cancer: a randomized, multicenter phase III trial. *J Clin Oncol* 2004; **22**: 2602–9.
10 Vasey P, Jayson G, Gordon A *et al.* Phase III randomized trial of docetaxel–carboplatin versus paclitaxel–carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst* 2004; **96**: 1682–91.
11 Dreyfuss AI, Clark JR, Norris CM *et al.* Docetaxel: an active drug for squamous cell carcinoma of the head and neck. *J Clin Oncol* 1996; **14**: 1672–8.
12 Van Cutsem E, Moiseyenko VM, Tjulandin S *et al.* Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24**: 4991–7.
13 Petrylak DP, Tangen CM, Hussain MHA *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; **351**: 1513–20.
14 Tannock IF, de Wit R, Berry WR *et al.* Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; **351**: 1502–12.
15 Muro K, Hamaguchi T, Ohtsu A *et al.* A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. *Ann Oncol* 2004; **15**: 955–9.
16 Bruno R, Vivier N, Vergniol JC *et al.* A population pharmacokinetic model for docetaxel (Taxotere), model building and validation. *J Pharmacokin Biopharm* 1996; **24**: 153–72.
17 Bruno R, Hille D, Riva A *et al.* Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. *J Clin Oncol* 1998; **16**: 187–96.
18 Tanigawara Y, Sasaki Y, Otsu T *et al.* Population pharmacokinetics of docetaxel in Japanese patients. *Proc Am Soc Clin Oncol* 1996; **15**: 479.
19 Vergniol J, Bruno R, Montay G, Frydman A. Determination of Taxotere in human plasma by a semi-automated high-performance liquid chromatographic method. *J Chromatogr* 1992; **582**: 273–8.
20 Ette EI. Stability and performance of a population pharmacokinetic model. *J Clin Pharmacol* 1997; **37**: 486–95.
21 Efron B. Bootstrap methods: another look at the jackknife. *Ann Stat* 1979; **7**: 1–26.
22 Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. *Stat Sci* 1986; **1**: 54–77.
23 Minami H, Ohe Y, Niho S *et al.* Comparison of pharmacokinetics and pharmacodynamics of docetaxel and cisplatin in elderly and non-elderly patients: why is toxicity increased in elderly patients? *J Clin Oncol* 2004; **22**: 2901–8.
24 ten Tije AJ, Verweij J, Carducci MA *et al.* Prospective evaluation of the pharmacokinetics and toxicity profile of docetaxel in the elderly. *J Clin Oncol* 2005; **23**: 1070–7.
25 Williams PJ, Ette EI. The role of population pharmacokinetics in drug development in light of the Food and Drug Administration's 'Guidance for industry: population pharmacokinetics.' *Clin Pharmacokinet* 2000; **39**: 385–95.

doi: 10.1111/j.1349-7006.2009.00992.x

26 Lee CKK, Rowinsky EK, Li J *et al.* Population pharmacokinetics of troxacitabine, a novel dioxolane nucleoside analogue. *Clin Cancer Res* 2006; 12: 2158–65.
27 Blair EYL, Rivory LP, Clarke SJ, McLachlan AJ. Population pharmacokinetics of raltitrexed in patients with advanced solid tumours. *Br J Clin Pharmacol* 2004; 57: 416–26.
28 Bruno R, Washington CB, Lu J-F *et al.* Population pharmacokinetics of trastuzumab in patients with HER2+ metastatic breast cancer. *Cancer Chemother Pharmacol* 2005; 56: 361–9.
29 Schmidli H, Peng B, Riviere GJ *et al.* Population pharmacokinetics of imatinib mesylate in patients with chronic-phase chronic myeloid leukaemia: results of a phase III study. *Br J Clin Pharmacol* 2005; 60: 35–44.
30 Boni JP, Leister C, Bender G *et al.* Population pharmacokinetics of CCI-779: Correlations to safety and pharmacogenomic responses in patients with advanced renal cancer. *Clin Pharmacol Ther* 2005; 77: 76–89.
31 van Kesteren C, Mathot RAA, Raymond E *et al.* Population pharmacokinetics of the novel anticancer agent E7070 during four phase I studies: model building and validation. *J Clin Oncol* 2002; 20: 4065–73.

original article

Annals of Oncology 20: 1210–1215, 2009
doi:10.1093/annonc/mdn781
Published online 2 March 2009

Phase III trial of doxorubicin plus cyclophosphamide (AC), docetaxel, and alternating AC and docetaxel as front-line chemotherapy for metastatic breast cancer: Japan Clinical Oncology Group trial (JCOG9802)

N. Katsumata[1]*, T. Watanabe[2], H. Minami[3], K. Aogi[4], T. Tabei[5], M. Sano[6], N. Masuda[7], J. Andoh[8], T. Ikeda[9], T. Shibata[10] & S. Takashima[4]

[1]*Department of Medical Oncology, National Cancer Center Hospital, Tokyo;* [2]*Department of Medical Oncology, Hamamatsu Oncology Center, Hamamatsu;* [3]*Department of Medicine, Kobe University Graduate School of Medicine, Kobe;* [4]*Department of Breast Oncology, Shikoku Cancer Center, Matsuyama;* [5]*Department of Medical Oncology, Saitama Cancer Center, Saitama;* [6]*Department of Breast Surgery, Niigata Breast Exam Center, Niigata;* [7]*Department of Surgery, Osaka National Hospital, Osaka;* [8]*Department of Breast Surgery, Tochigi Cancer Center, Utsunomiya;* [9]*Department of Surgery, Teikyo University Hospital and* [10]*Japan Clinical Oncology Group Data Center, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan*

Received 11 September 2008; revised 12 December 2008; accepted 12 December 2008

Background: This randomized, multicenter, phase III trial compared doxorubicin plus cyclophosphamide (AC), single-agent docetaxel (D), and an alternating regimen of AC and docetaxel (AC–D) as first-line chemotherapy in metastatic breast cancer (MBC).

Patients and methods: Patients with MBC resistant to endocrine therapy were entered in a randomized study to receive either six cycles of AC (doxorubicin 40 mg/m^2 plus cyclophosphamide 500 mg/m^2), D (60 mg/m^2), or alternating treatment with AC–D (i.e. three cycles of AC and three cycles of D). Treatment was administered every 3 weeks.

Results: A total of 441 patients were entered in a randomized study. Response rates were 30% for AC, 41% for D, and 35% for AC–D. The median times to treatment failure (TTFs) were 6.4, 6.4, and 6.7 months (one-sided log-rank test, $P = 0.13$ for AC versus D, $P = 0.14$ for AC versus AC–D) and median overall survival (OS) was 22.6, 25.7, and 25.0 months ($P = 0.09$ for AC versus D, $P = 0.13$ for AC versus AC–D) in the AC, D, and AC–D, respectively.

Conclusion: There was no difference in the TTF among the three arms. However, there was a trend toward a better response and better OS in the D than in the AC.

Key words: cyclophosphamide, docetaxel, doxorubicin, metastatic breast cancer, phase III

introduction

Metastatic breast cancer (MBC) is unlikely to be cured by currently available treatment; however, systemic therapy can provide symptomatic relief and prolong survival [1]. Cytotoxic chemotherapy is generally the treatment option of choice in patients with hormone receptor-negative disease, patients whose disease has become resistant to hormonal therapy, and patients in whom impending organ failure necessitates rapid tumor shrinkage. Anthracycline monotherapy or combination therapy has been used as first-line treatment of MBC for over 30 years. Although anthracycline-based chemotherapy remains the standard treatment, several toxic effects can limit its usefulness in a palliative setting.

Docetaxel was introduced for the treatment of advanced breast cancer in the 1990s. Single-agent docetaxel is very active against advanced breast cancer. Four large randomized phase III trials have compared anthracycline-based regimens with docetaxel-based regimens as first-line treatment of MBC. Chan et al. [2] compared single-agent docetaxel with single-agent doxorubicin and reported higher response rates and a longer time to progression (TTP) with docetaxel, but no difference in survival. Nabholtz et al. [3] compared doxorubicin plus docetaxel with doxorubicin plus cyclophosphamide (AC). The former had higher response rates and a longer TTP, but did not improve survival. Mackey et al. [4] compared a combination of docetaxel, doxorubicin, and cyclophosphamide (TAC) with 5-fluorouracil plus doxorubicin plus cyclophosphamide (FAC). TAC had a higher response rate, but there was no difference in either TTP or survival. To date, only one study, carried out by Bontenbal et al. [5], showed that doxorubicin plus docetaxel is superior to FAC in terms of response rate, TTP, and survival.

Correspondence to: Dr N. Katsumata, Department of Medical Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.
Tel: +81-3-3542-2511; Fax: +81-3-3542-3815; E-mail: nkatsuma@ncc.go.jp

Because these trials failed to reach clear-cut conclusions, the optimal regimen for first-line chemotherapy in patients with MBC remains controversial.

Alternating chemotherapy is an approach designed to produce maximal antitumor activity by alternating non-cross-resistant regimens of chemotherapy [6]. Alternating chemotherapy has been suggested to be effective in Hodgkin's disease and small-cell lung cancer [7, 8]. In breast cancer, the use of alternating chemotherapy remains controversial because a previous study showed that alternating doxorubicin and CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) produced no clinical benefit [9]. To clarify the clinical benefits of single-agent docetaxel and an alternating regimen including doxorubicin and docetaxel, we carried out a randomized clinical trial in which patients were randomly assigned to receive a conventional regimen of AC, docetaxel alone (D), or an alternating regimen of AC and docetaxel (AC–D) as first-line chemotherapy for MBC. The dose of docetaxel was 60 mg/m^2, based on the results of a Japanese phase II trial [10]. Because this study was designed to evaluate the clinical benefits of first-line treatment independently of the effects of second-line crossover treatment, we designated the time to treatment failure (TTF) as the primary end point.

patients and methods

eligibility criteria

Patients were eligible if they had histologically proven MBC that was resistant to hormonal therapy, such as disease that was estrogen receptor negative, failed to respond to hormonal therapy, or relapsed within 6 months after adjuvant hormonal therapy. Patients who had received adjuvant chemotherapy were eligible, except for those who had recurrence within 6 months after the end of anthracycline-based adjuvant chemotherapy. Patients who had previously received anthracyclines for the treatment of MBC and those who had previously received taxanes were excluded. Eligible patients had to have lesions that could be measured or assessed, an age between 20 and 75 years, an Eastern Cooperative Oncology Group performance status of zero to three, and the following laboratory values: white cell count ≥4000/μl or absolute neutrophil count ≥2000/μl, platelets ≥100 000/μl, aspartate aminotransferase and alanine aminotransferase ≤1.5× the upper limit of normal or ≤60 IU/l, total bilirubin concentration ≤1.5 mg/dl, creatinine clearance ≤1.5 mg/dl, and a normal electrocardiogram or minimum abnormalities requiring no treatment. Patients with any of the following conditions were excluded from the study: pregnancy; malignant pleural effusion, ascites, or pericardial effusion that required emergency treatment; active infections; synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*; previous stem-cell transplantation; brain metastasis requiring emergency treatment; a history of receiving >250 mg/m^2 of anthracyclines; cardiac disease of New York Heart Association class II or higher; a history of drug hypersensitivity; interstitial pneumonitis or pulmonary fibrosis; positive surface antigen of hepatitis B virus (HBsAg); positive hepatitis C virus (HCV) (deleted by amendment on 29 May 2002); and treatment with antipsychotic medication. All patients gave informed consent before enrollment. The study protocol was approved by the institutional review boards at the participating institutions.

study design

This was a randomized, multicenter, nonblinded phase III study. The randomization of treatment assignments was centralized. After confirming that candidate subjects met all the inclusion and exclusion criteria, the Japan Clinical Oncology Group (JCOG) Data Center was informed by telephone or fax. Enrolled patients were then randomly assigned to one of the three treatment groups by the minimization method, balancing the arms according to disease status (stage IV versus recurrent disease), prior anthracyclines, liver metastasis, and institution.

treatment schedule

The treatment scheme is shown in Figure 1. Patients were randomly assigned to receive doxorubicin 40 mg/m^2 plus cyclophosphamide 500 mg/m^2 (AC) every 3 weeks for six cycles; docetaxel 60 mg/m^2 (D), administered by i.v. infusion over the course of 1 h every 3 weeks for six cycles; or AC and D in the same doses, administered alternately every 3 weeks for a total three cycles of AC and three cycles of D (alternating AC–D).

Dexamethasone was given in an i.v. dose of 8 mg 1 h before docetaxel and in an oral dose of 4 mg 12, 24, 36, and 48 h after infusion. Antiemetics were used at the investigator's discretion. On treatment failure or disease

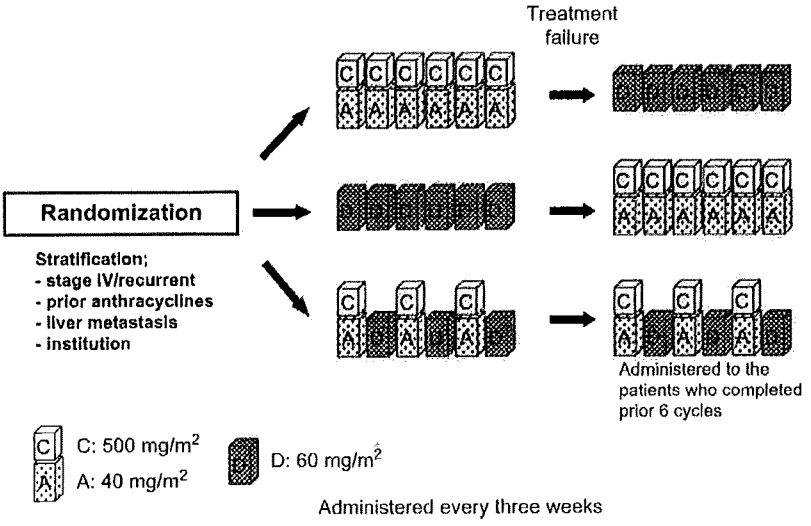


Figure 1. Schema of the trial. C, cyclophosphamide; A, doxorubicin; D, docetaxel.

doi:10.1093/annonc/mdn781 | 1211

progression during or after treatment, patients were crossed over from AC to D or from D to AC. The alternating AC–D regimen was restarted at the time of disease progression in patients who had completed six cycles of first-line AC–D.

Treatment was delayed for up to 3 weeks in the event of toxicity, but was restarted when laboratory values returned to the following values: white cell count ≥3000/μl or absolute neutrophil count ≥1500/μl, platelet count ≥100 000/μl, aspartate aminotransferase and alanine aminotransferase <1.5× the upper limit of normal or ≤60 IU/l, and creatinine clearance ≤1.5 mg/dl. Dose reduction (40–30 mg/m^2 doxorubicin and 500–400 mg/m^2 cyclophosphamide for AC and 60–50 mg/m^2 for D) was implemented when febrile neutropenia, grade 4 thrombocytopenia, or grade 3 non-hematologic toxicity (except nausea and vomiting) occurred. Treatment was terminated in the event of any grade 4 non-hematologic toxicity. Doses that were reduced because of toxicity could not be reincreased. Granulocyte colony-stimulating factor (filgrastim or lenograstim) could be used if the absolute neutrophil count fell to <500/μl or if febrile neutropenia developed.

assessments

Prestudy evaluations included a complete medical history, physical examination, complete blood cell counts, serum chemical analysis, tumor markers (carcinoembryonic antigen and CA15-3), chest radiography and/or computed tomography (CT), bone scintigraphy (and if positive, bone radiography), and abdominal CT or ultrasonography. All lesions that could be measured or assessed were evaluated at least twice, during first- and second-line chemotherapy, respectively. Response was classified according to the criteria of the Japanese Research Society for Breast Cancer, which are similar to the World Health Organization criteria. Objective responses were confirmed by central review at regular group meetings. Toxic effects were evaluated according to the JCOG Toxicity Criteria [11]. These criteria were based on the National Cancer Institute—Common Toxicity Criteria. As a pilot study to evaluate the feasibility of treatment, quality of life (QoL) was assessed during first-line chemotherapy for the first 50 patients randomly assigned to each arm, using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire. QoL was assessed at baseline and 6 and 18 weeks after treatment had begun.

statistical considerations

The primary end point of this trial was the TTF. The secondary end points were overall survival (OS), progression-free survival (PFS), response rate, and adverse events. TTF was calculated from the date of randomization to the date of first documentation of discontinuation of first-line chemotherapy, disease progression, or death from any cause. Data on patients who were alive without treatment failure were censored on the date on which they were last known to be alive. PFS was calculated from the date of randomization to the date of the first documentation of disease progression or death from any cause. Data on patients who were alive without progression were censored on the date on which they were last known to be alive. OS was calculated from the date of randomization to the date of death from any cause. Data on patients who were alive were censored at the time of the last follow-up visit.

Our hypothesis was that D or alternating AC–D would prolong TTF as compared with AC. We assumed that the median TTF in the AC arm would be 7 months and that D or alternating AC–D would improve the TTF by 3.5 months. To adjust for multiplicity associated with two-pair comparisons of AC versus D and AC versus alternating AC–D, the planned sample size was 147 patients for each treatment arm, with a one-sided alpha of 0.025, a power of 0.9, an accrual of 3 years, and a follow-up of 1 year. The target number of patients was thus 450. Interim analysis was planned when 300 patients had been randomly assigned treatment. Multiplicity by multiple look was adjusted with the use of the O'Brien–Fleming alpha-spending function. The intention-to-treat (ITT) population was defined as all patients who were randomly assigned treatment. TTF, PFS, and OS were analyzed for the ITT population and compared among the treatment arms by the log-rank test. Response and safety analyses were carried out for assessable patients. As a pilot study, QoL was assessed in the initially enrolled 150 patients to evaluate the feasibility of treatment. Scores were calculated according to the scoring guidelines for FACT-B, and changes from baseline scores were compared between the treatment arms by unpaired Student's *t*-tests. All analyses were carried out with SAS software, version 8.2 (SAS Institute, Cary, NC).

results

patient characteristics

From January 1999 to May 2003, a total of 441 patients were enrolled at 29 institutions. We extended the accrual time from 3 to 4 years because enrollment was slower than expected. In May 2003, we stopped enrollment on reaching a sufficient number of events for analysis. Twenty-four patients were ineligible: 16 lacked a sufficient interval from the completion of previous treatment; one had breast sarcoma; five had positive or unknown test results for HBsAg or HCV; one had previously received an anthracycline for MBC; and one had double cancer. Of the 441 patients, 146 were assigned to the AC arm, 147 were assigned to the D arm, and 148 were assigned to the alternating AC–D arm. All major prognostic factors were well balanced among the treatment arms (Table 1).

Table 1. Patient characteristics

Characteristic	AC (n = 146)	D (n = 147)	AC–D (n = 148)
Age (years)			
Median	54	54	56
Range	26–72	28–74	27–75
PS (%)			
0	71	70	68
1	25	25	26
2	3	3	5
3	1	1	1
Disease status (%)			
Stage IV	19	21	20
Recurrent	81	79	80
ER status (%)			
Negative	56	56	57
Positive	35	35	34
Unknown	8	8	9
Adjuvant chemotherapy (%)	58	59	58
Adjuvant anthracyclines (%)	15	16	18
Adjuvant hormonal therapy (%)	50	54	50
Hormonal therapy for MBC (%)	43	42	45
Radiotherapy for MBC (%)	19	14	19
Metastatic sites (%)			
Liver	23	24	23
Lung	48	43	41
Bone	37	37	33

AC, doxorubicin and cyclophosphamide; D, docetaxel; AC–D, alternating AC and docetaxel; PS, performance status; ER, estrogen receptor; MBC, metastatic breast cancer.

More than half of all patients had received adjuvant chemotherapy, although the proportion of patients previously treated with adjuvant anthracyclines was relatively low.

treatment

Sixty-eight percent of the patients in the AC arm completed six cycles of treatment versus 76% in the D arm and 77% in the alternating AC–D arm (Table 2). The higher rate of discontinuing the protocol treatment in the AC arm than in the D arm and the alternating AC–D arm was mainly attributed to disease progression. The proportions of patients who discontinued due to toxicity or refused to continue treatment were low. Five patients assigned to alternating AC–D (3%) were mistakenly given the wrong sequence of chemotherapy by the physician in charge. Ten patients had protocol violations: six did not undergo adequate blood tests before chemotherapy; three received nonprotocol surgery after chemotherapy, but before disease progression; and one received nonprotocol concurrent irradiation with chemotherapy.

toxicity

Grade 3 or 4 leukopenia and neutropenia occurred frequently in the D arm and the alternating AC–D arm, and febrile neutropenia most frequently occurred in the alternating AC–D arm (Table 3). Non-hematologic toxic effects were mild in all three treatment arms. There was no treatment-related death. Grade 3 or 4 nausea and vomiting were more frequent in the AC arm and alternating AC–D arm than in the D arm. One patient had grade 4 diarrhea in the alternating AC–D arm, and acute myelogenous leukemia developed in one patient assigned to the D arm after 3 months of second-line AC.

response to treatment

Tumor response was assessed in all patients randomly assigned to treatment. The responses to first-line and the second-line chemotherapy are shown in Table 4. Objective responses to first-line chemotherapy were observed in the 29% of patients with AC arm, 40% of patients with D arm, and 35% of patients with alternating AC–D arm ($P = 0.05$ for AC versus D and $P = 0.32$ for AC versus alternating AC–D). The duration of response did not differ among the three treatment arms. The numbers of patients who received second-line chemotherapy after treatment failure following first-line chemotherapy were similar in the AC arm (82%, 119 of 146 patients) and the D arm (80%, 117 of 147); only 57% of patients in the alternating AC–D arm (84 of 148) received second-line alternating AC–D regimens. The responses to second-line chemotherapy were observed in the 24% of patients receiving D, 20% of patients receiving AC, and 20% of patients receiving alternating AC–D ($P = 0.53$ for AC versus D and $P = 0.61$ for AC versus alternating AC–D). The proportion of patients with progressive disease was higher in the AC arm than in the other arms. The response rates were calculated on the basis of the results of central review.

Table 2. Reasons for off-treatment of first-line chemotherapy

	% Over total		
	AC ($n = 146$)	D ($n = 147$)	AC–D ($n = 148$)
Completed	68	76	77
Progression	25	18	15
Toxicity	2	2	1
Patient refusal	1	1	1
Physician's decision	1	1	3
Others	1	3	3

AC, doxorubicin and cyclophosphamide; D, docetaxel; AC–D, alternating AC and docetaxel.

Table 3. Grade3/4 toxic effects in first-line chemotherapy

	%		
	AC ($n = 146$)	D ($n = 147$)	AC–D ($n = 146$)
Leukopenia	21	34	34
Neutropenia[a]	26	45	46
Anemia	3	1	3
Febrile neutropenia	3	4	6
Nausea and vomiting	3	1	4
Diarrhea	0	1	1
Stomatitis	1	0	0
Hypersensitivity	0	1	1

[a]Neutrophil counts were missed in three patients with both AC and D arm and in four patients with AC–D arm.
AC, doxorubicin and cyclophosphamide; D, docetaxel; AC–D, alternating AC and docetaxel.

Table 4. Responses

First-line chemotherapy	AC ($n = 146$)	D ($n = 147$)	AC–D ($n = 148$)
Complete response (%)	7	5	3
Partial response (%)	22	35	31
Overall (%)	29	40	35
95% CI (%)	22–37	32–49	27–43
No change (%)	40	37	46
Progressive disease (%)	26	18	16
Not assessable (%)	5	4	4
Response duration (months)	9	9.2	9.2
95% CI (%)	7.6–10.8	7.9–10.0	7.2–10.4
Second-line chemotherapy	**D ($n = 119$)**	**AC ($n = 117$)**	**AC–D ($n = 84$)**
Complete response (%)	3	4	5
Partial response (%)	20	15	16
Overall (%)	24	20	20
95% CI (%)	16–32	13–28	12–30
No change (%)	39	36	48
Progressive disease (%)	35	40	27
Not assessable (%)	3	5	5

AC, doxorubicin and cyclophosphamide; D, docetaxel; AC–D, alternating AC and docetaxel; CI, confidence interval.

survival

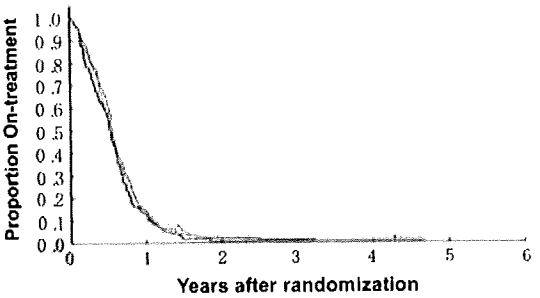
Kaplan–Meier curves for TTF after the start of first-line chemotherapy were plotted on the basis of data available as of June 2004. TTF data were available for 437 of the 441 patients who were randomly assigned to treatment. Follow-up case report forms were not available for the other four patients (Figure 2). There was no significant difference among the arms: median TTF was 6.4 months in the AC arm and D arm and 6.7 months in the alternating AC–D arm. There was also no significant difference in TTF after multivariate adjustment for known prognostic factors, carried out with a Cox model. PFS also did not differ significantly: median PFS was 6.6 months [95% confidence interval (CI) 6.0–7.3] in the AC arm, 7.0 months (95% CI 6.2–7.9) in the D arm, and 7.1 months (95% CI 6.6–7.8) in alternating AC–D arm (one-sided log-rank test, $P = 0.19$ for arm AC versus D, $P = 0.11$ for arm AC versus AC–D). Primary OS was analyzed at the same time as TTF (June 2004). The median survival times were 22.4 months (95% CI 18.0–27.0) in the AC arm, 25.7 months (95% CI 20.9–31.7) in the D arm, and 25.0 months (95% CI 20.9–31.0) in the alternating AC–D arm ($P = 0.09$ for arm AC versus D, $P = 0.08$ for arm AC versus AC–D). An updated OS analysis carried out in June 2006 showed trends toward better median survival times in the D arm and alternating AC–D arm than in the AC arm (one-sided log-rank test, $P = 0.09$ for arm AC versus D, $P = 0.13$ for arm AC versus AC–D; Figure 3).

quality of life

QoL was assessed according to the FACT-B scale at baseline and 6 and 18 weeks after treatment had begun in the first 150 patients. Completed questionnaires were received from 99% of the patients (148 of 150) at baseline, 89% (134 of 150) at 6 weeks, and 87% (130 of 150) at 18 weeks. The maximum possible FACT-B score is 152 points; a higher score indicates a better QoL. The median scores at baseline were 93.1 (range 51.1–131.4), 105.9 (range 52.6–140.0), and 104.5 (range 38.6–141.0) in the AC arm, the D arm, and the AC–D arm, respectively. The median scores were 90.0 (range 44.0–127.0), 96.3 (range 45.0–133.0), and 96.3 (range 41.9–135.6) at 6 weeks, and 95.0 (range 56.4–139.0), 91.3 (range 34.8–144.0), and 94.1 (range 49.9–132.0) at 18 weeks, respectively. There was no statistically significant difference among the three treatment arms.

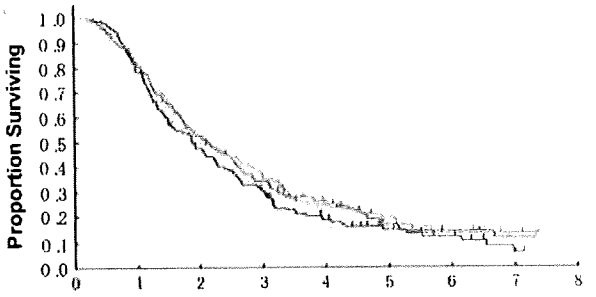
discussion

We compared AC, single-agent D, and alternating AC–D as first-line chemotherapy for MBC. Although the primary end point of TTF did not differ significantly between the D arm or the alternating AC–D arm and the AC arm, there was a trend toward a higher response rate and better OS in the D arm than in the AC arm. On treatment failure or disease progression during or after treatment, patients were crossed over from AC to D or from D to AC. In the AC–D arm, the same regimen was resumed. The rate of response to first-line chemotherapy as well second-line chemotherapy was higher in the D arm than in either the AC arm or alternating AC–D arm. Interestingly, patients continued to respond to second-line treatment with



	n	No. of event	Median TTF (95%CI)	Log-rank (1-sided)
– AC to D	143	139	6.4 months (5.6-7.1)	-
D to AC	147	143	6.4 months. (5.8-7.3)	$P = 0.13$
AC-D	147	146	6.7 months (6.2-7.2)	$P = 0.14$

Figure 2. Time to treatment failure of the first-line chemotherapy. AC, doxorubicin and cyclophosphamide; D, docetaxel; AC–D, alternating AC and docetaxel.



	n	No. of events	Median OS (95% CI)	Log-rank
– AC	146	125	22.6 months (18.0-27.1)	-
D	147	117	25.7 months (21.5-31.7)	$P = 0.09$
AC-D	148	120	25.0 months (21.2-30.5)	$P = 0.13$

Figure 3. Overall survival. AC, doxorubicin and cyclophosphamide; D, docetaxel; AC–D, alternating AC and docetaxel.

the same alternating AC–D regimen. Improved OS observed is usually associated with improved TTF and PFS. In this study, however, there was a trend toward better OS in the D arm, but no significant difference in TTF or PFS. There were also no differences in potential confounding factors, such as salvage therapy or non-cancer-related death. Our results are consistent with the findings of a meta-analysis of taxanes based on all relevant clinical trials of first-line treatment in MBC, which showed that single-agent taxanes were worse than single-agent anthracyclines in terms of TTP, but not in terms of response rates or survival [12]. A systematic review of the Cochrane Database showed that taxane-based regimens were significantly better than non-taxane-based regimens for MBC in terms of OS, TTP, and overall response [13]. On subgroup analysis, D was associated with significantly improved OS, TTP, and overall response, whereas paclitaxel was not. Our results agree with these findings.

When used as a single agent, docetaxel is generally used in a dose of 100 mg/m^2 in Western countries. We used a lower dosage of 60 mg/m^2 for single-agent docetaxel because this is

the approved dose for the treatment of MBC in Japan based on the results of a phase II trial [10]. This low dose of docetaxel might have led to the nonsignificant differences among the treatment arms in our study. A recent randomized phase III trial [14] comparing 60, 75, and 100 mg/m^2 of docetaxel in women with MBC reported a significant relation between dose and response rate, but no significant difference in TTP or OS; moreover, the incidence and severity of adverse events were higher in the high-dosage group. The optimal dosage of docetaxel for MBC thus requires further study.

Alternating chemotherapy is one of the promising approaches to improve the response to chemotherapy. In breast cancer, Bonadonna et al. [9] reported that alternating chemotherapy with doxorubicin and CMF was not superior to sequential chemotherapy with doxorubicin followed by CMF. Because docetaxel is a promising drug of non-cross resistance to doxorubicin, we studied the response to different sequences of AC and D. Our trial suggested that both single-agent D and alternating AC–D were slightly superior to AC; however, the effectiveness of AC–D did not warrant the complexity of this regimen, and D might be a better regimen in terms of simplicity. These results suggest that single-agent docetaxel is the most promising candidate for first-line chemotherapy.

In conclusion, this phase III trial demonstrated that docetaxel alone was associated with a trend toward better response and OS than AC, with no significant difference in TTF or PFS. The survival benefits of first-line treatment with single-agent docetaxel should be reevaluated in further randomized phase III trials with OS as the primary end point.

funding

Cancer Research (11S-1, 14S-1, 17S-1) from the Ministry of Health, Labour and Welfare, Japan.

acknowledgements

The authors' thanks go to T. Asakawa and N. Ishizuka for statistical support; K. Minamoto, M. Yamauchi, and H. Kaba for data management; and Haruhiko Fukuda and Akihiro Sato for manuscript writing and interpretation. This study was presented in abstract form at the Annual Meeting of the American Society of Clinical Oncology, 16 May 2005. The following institutions participated in this study: Hokkaido Cancer Center, Sapporo; Tochigi Cancer Center; Gunma Cancer Center; Saitama Cancer Center; National Cancer Center Hospital East; National Cancer Center Hospital; Chiba Cancer Center; Tokyo Metropolitan Komagome Hospital; National International Medical Center; Tokyo Medical Center; Keio University; St. Luke's International Hospital; Tokai University; Niigata Cancer Center, Niigata Hospital; Hamamatsu Medical Center; Shizuoka General Hospital; International University of Health and Welfare Atami Hospital; Aichi Cancer Center; Nagoya Medical Center; Kinki University; National Hospital Organization Osaka National Hospital; Kansai Rosai Hospital; Kawasaki Medical School; Kure Medical Center; Fukuyama Medical Center; Sikoku Cancer Center; Kyushu Cancer Center; Kitakyushu Municipal Medical Center and Nagasaki Medical Center.

references

1. Gennari A, Conte P, Rosso R et al. Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. Cancer 2005; 104: 1742–1750.
2. Chan S, Friedrichs K, Noel D et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol 1999; 17: 2341–2354.
3. Nabholtz JM, Falkson C, Campos D et al. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J Clin Oncol 2003; 21: 968–975.
4. Mackey JR, Paterson A, Dirix L, Dewar J. Final results of the phase III randomised trial comparing docetaxel (T), doxorubicin (A) and cyclophosphamide (C) to FAC as first line chemotherapy (CT) for patients (pts) with metastatic breast cancer (MBC). Proc Am Soc Clin Oncol 2002; 21: 35a (Abstr 137).
5. Bontenbal M, Creemers GJ, Braun HJ et al. Phase II to III study comparing doxorubicin and docetaxel with fluorouracil, doxorubicin, and cyclophosphamide as first-line chemotherapy in patients with metastatic breast cancer: results of a Dutch Community Setting Trial for the Clinical Trial Group of the Comprehensive Cancer Centre. J Clin Oncol 2005; 23: 7081–7088.
6. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 1979; 63: 1727–1733.
7. Evans WK, Feld R, Murray N et al. Superiority of alternating non-cross-resistant chemotherapy in extensive small cell lung cancer. A multicenter, randomized clinical trial by the National Cancer Institute of Canada. Ann Intern Med 1987; 107: 451–458.
8. Fukuoka M, Furuse K, Saijo N et al. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. J Natl Cancer Inst 1991; 83: 855–861.
9. Bonadonna G, Valagussa P, Santoro A. Alternating non-cross-resistant combination chemotherapy or MOPP in stage IV Hodgkin's disease. A report of 8-year results. Ann Intern Med 1986; 104: 739–746.
10. Adachi I, Watanabe T, Takashima S et al. A late phase II study of RP56976 (docetaxel) in patients with advanced or recurrent breast cancer. Br J Cancer 1996; 73: 210–216.
11. Tobinai K, Kohno A, Shimada Y et al. Toxicity grading criteria of the Japan Clinical Oncology Group. The Clinical Trial Review Committee of the Japan Clinical Oncology Group. Jpn J Clin Oncol 1993; 23: 250–257.
12. Piccart-Gebhart MJ, Burzykowski T, Buyse M et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol 2008; 26: 1980–1986.
13. Ghersi D, Wilcken N, Simes RJ. A systematic review of taxane-containing regimens for metastatic breast cancer. Br J Cancer 2005; 93: 293–301.
14. Harvey V, Mouridsen H, Semiglazov V et al. Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. J Clin Oncol 2006; 24: 4963–4970.

another disease by using the dynamic CT scan with contrast medium. In diagnostic imaging, ACC is similar to the PA for a solid and hypovascular tumor.[5] However, some ACC were hypervascular tumors compared with PA. Therefore, if the pancreatic lesion is hypervascular, we would suspect the ACC.

The ACC was characterized by a gray or brown, solid, lobulated, and well-circumscribed mass with central necrosis, and the tumor showed a mixed pattern, with acinar pattern, reminiscent of normal pancreatic acinar tissue, alternating with trabecular and solid formations histopathologically. Acinar cell carcinoma had a positive reaction to trypsin staining for 100% and to lipase staining for 77%, in contrast, two thirds of ACC had negative chymotrypsin and amylase staining.[6] In our case, it was difficult to diagnose ACC by only cytology, and 1 reason for the poor prognosis in our case was that it was not confirmed by the transthoracic needle biopsy.

In a retrospective study of 672 ACC cases, the MST of ACC was 47 months and was better than 4 months of PA. In particular, the MST of unresected ACC was 25 months better than 3 months of PA.[2] Wisnoski et al[3] pointed out the biological differentiation between the ACC and PA. However, in their study, there was no data about the effect of chemotherapy and its regimens. There have been few case reports until now. Aoki et al[7] reported a case that was affected by the combination therapy with gemcitabine and radiotherapy, and Kataoka et al[8] reported a case that responded to a combination therapy with cisplatin and S-1 in Japan. Our case was treated with gemcitabine and cisplatin, which was reported to have a good response to ACC, however, the patient had a poor prognosis.

A solitary spleen metastasis is a rare event and fewer than 20 cases have been reported.[4] Metastasis from colon cancer, endometrial cancer, and melanoma have been documented, however, metastasis from pancreas (especially ACC) has never been reported until now. Furthermore, spontaneous splenic rupture from metastatic solid tumors are exceedingly rare. Massarweh et al[4] and Gupta and Harvey[9] reported the spontaneous rupture of spleen secondary to metastasis in lung cancer, and every case had a poor prognosis. In addition, in our case, after the splenic rupture, the patient's condition deteriorated rapidly, and he died 12 weeks later.

We report the first case of spontaneous splenic rupture due to ACC in the pancreas. Because of the unusual clinical course, we initially made the diagnosis of lung cancer. The diagnosis of ACC was made only after autopsy.

Katsutoshi Ando, MD
Yoshihiro Ohkuni, MD
Norihiro Kaneko, MD
Department of Pulmonary Medicine
Kameda Medical Center
Kamogawa, Chiba, Japan
ankatu1019@yahoo.co.jp
Makoto Narita, MD
Department of Pathology
Kameda Medical Center
Kamogawa, Chiba, Japan

REFERENCES

1. Pancreatic Cancer Registry in Japan: 20 years of experience. *Pancreas*. 2004;28:210–230.
2. Sumii T, Funakoshi K, Nishiyama K. Acinar cell carcinoma of pancreas. *Liver Gall Bladder Pancreas*. 2004;49:676–681.
3. Wisnoski NC, Townsend CM Jr, Nealon WH, et al. 672 patients with acinar cell carcinoma of the pancreas: a population-based comparison to pancreatic adenocarcinoma. *Surgery*. 2008;144:141–148.
4. Massarweh S, Dhingra H. Solitary splenic metastasis in lung cancer with spontaneous rupture. *J Clin Oncol*. 2001;19:1574–1575.
5. Chiou YY, Chiang JH, Hwang JI, et al. Acinar cell of pancreas: clinical and computed tomography manifestations. *J Comput Assist Tomogr*. 2004;28:180–186.
6. Morohoshi T, Kanda M, Horie A, et al. Immunocytochemical markers of uncommon pancreatic tumors. *Cancer*. 1987;15:739–747.
7. Aoki H, Shiozaki Y, Harano M, et al. A case of unresected acinar cell carcinoma that was effected radiotherapy in combination with chemotherapy. *Tan to Sui*. 2008;29:369–373.
8. Kataoka Y, Nio Y, Yano S, et al. Pancreatic acinar cell carcinoma successfully treated with combination of oral TS-1 and intra-arterial cisplatin. *Gan To Kagaku Ryoho*. 2006;33:525–528.
9. Gupta PB, Harvey L. Spontaneous rupture of the spleen secondary to metastatic carcinoma. *Br J Surg*. 1993;80:613.

Features of Gemcitabine-Related Severe Pulmonary Toxicity *Patients With Pancreatic or Biliary Tract Cancer*

To the Editor:

Gemcitabine (GEM) is a deoxycytidine analog in which 2 fluorine atoms have been inserted. Gemcitabine is inactive by itself, but once inside the cytoplasm of a cell, GEM is phosphorylated into diphosphate and triphosphate forms, which competes with 2′-deoxycytidine 5′-triphosphate (dCTP) for incorporation into DNA, where they block DNA synthesis.[1] Gemcitabine is active against pancreatic cancer,[2] biliary tract cancer.[3] In Japan, GEM was approved by the Japanese Ministry of Health, Labour and Welfare in April 2001 for use in patients with locally advanced or metastatic pancreatic cancer and in June 2006 for use in patients with advanced biliary tract cancer. Although GEM is generally well tolerated, life-threatening pulmonary toxicity has been described in rare case reports.[4–6] However, few reports have described the frequency, onset pattern, computed tomography (CT) imaging features of this complication.

MATERIALS AND METHODS

Between September 2002 and December 2007, 418 patients with pancreatic cancer or biliary tract cancer were treated with GEM at our institution and were subsequently enrolled in the present study. All the patients were treated with GEM alone or GEM in combination with S-1 or erlotinib. The dosage of GEM was 1000 mg/m^2, administered weekly for 3 out of every 4 weeks of treatment with GEM alone or GEM + erlotinib and for 2 out of every 3 weeks of treatment with GEM + S-1. Nine patients of the 418 patients subsequently developed severe pulmonary toxicity related to GEM. In our retrospective study, severe pulmonary toxicity related to GEM was defined as (1) the development of grade 3 or higher hypoxia and pneumonitis according to the Common Terminology Criteria for Adverse Events (CTCAE Version 3.0); (2) strong suspicion of pulmonary toxicity related to GEM based on clinical symptoms, laboratory data, and imaging results; or (3) chest x-ray images showing shadows with a diffuse ground glass appearance, and not infiltrative shadows.

Fisher exact test was used to compare the incidence of the severe pulmonary toxicity related to GEM according to potential predictors.

RESULTS

Between September 2002 and December 2007, 418 patients with pancreatic cancer or biliary tract cancer were treated with GEM, and 9 of the 418 patients subsequently developed severe pulmonary toxicity related to GEM. Among the patients treated with GEM, 340 patients had pancreatic cancer and 78 had biliary tract cancer, the median age was 64 years (range, 32–83 years), 260 were men and 158 were women, 239 had a history of

TABLE 1. Patient Characteristics and Incidence of Severe Pulmonary Toxicity

	Patients	Subjects	Incidence (%)	P
All patients	418	9	2.15	
Cancer type				
Pancreas	340	7	2.06	
Biliary duct	78	2	2.56	0.78
Sex				
Male	260	5	1.92	
Female	158	4	2.53	0.68
Smoking				
Yes	239	6	2.51	
No	179	3	1.68	0.56
Age				
<70	311	6	1.93	
≥70	107	3	2.80	0.59
Previous chemotherapy				
Yes	324	8	2.47	
No	94	1	1.06	0.40
Combination chemotherapy				
No	401	7	1.75	
Yes	17	2	11.76	0.005

smoking, 94 had a history of previous chemotherapy, 17 patients had been treated with combination chemotherapy.

Among the 9 patients who developed severe pulmonary toxicity, 7 patients had pancreatic cancer and 2 had biliary tract cancer, the median age was 65 years (range, 41–76 years), 5 were men, 6 had a history of smoking, 1 had a history of previous chemotherapy, and 2 had been treated with combination chemotherapy.

The incidence of severe pulmonary toxicity related to GEM was 2.15%. When examined according to subgroups, the incidences of severe pulmonary toxicity were as follows: (1) cancer type: pancreatic cancer, 2.06%; biliary duct cancer, 2.56%; $P = 0.78$; (2) sex: male, 1.92%; female, 2.53%, $P = 0.68$; (3) history of smoking: yes, 2.51%; no, 1.68%; $P = 0.56$; (4) age: younger than 70 years, 1.93%; 70 years or older, 2.80%; $P = 0.59$; (5) previous chemotherapy: yes, 1.06%; no, 2.47%; $P = 0.40$; and (6) combination chemotherapy: yes, 11.76%; no, 1.75%; $P = 0.005$. We show these data at Table 1.

Among the 9 patients with severe pulmonary toxicity related to GEM in this study, the frequent clinical descriptions were dyspnea (88.9%), fever (66.7%), fatigue (44.4%), and cough (33.3%). None of the patients had productive coughs.

The median total dosage of GEM among the 9 patients with severe pulmonary toxicity related to GEM was 11000 mg/m^2 (range, 1800–12,000 mg/m^2). The median time from the first administration to the appearance of toxicity findings on a chest x-ray was 106 days (range, 22–147 days), and the median time from the last administration to the onset appearance of toxicity findings on a chest x-ray was 14 days (range, 8–91 days).

The main chest x-ray finding was diffuse and bilateral shadows with ground glass appearance; the findings for all 9 patients showed this result, and none of the patients' images showed infiltrative shadows. Chest CT findings were available for 8 of the 9 patients; the main CT features of severe pulmonary toxicity

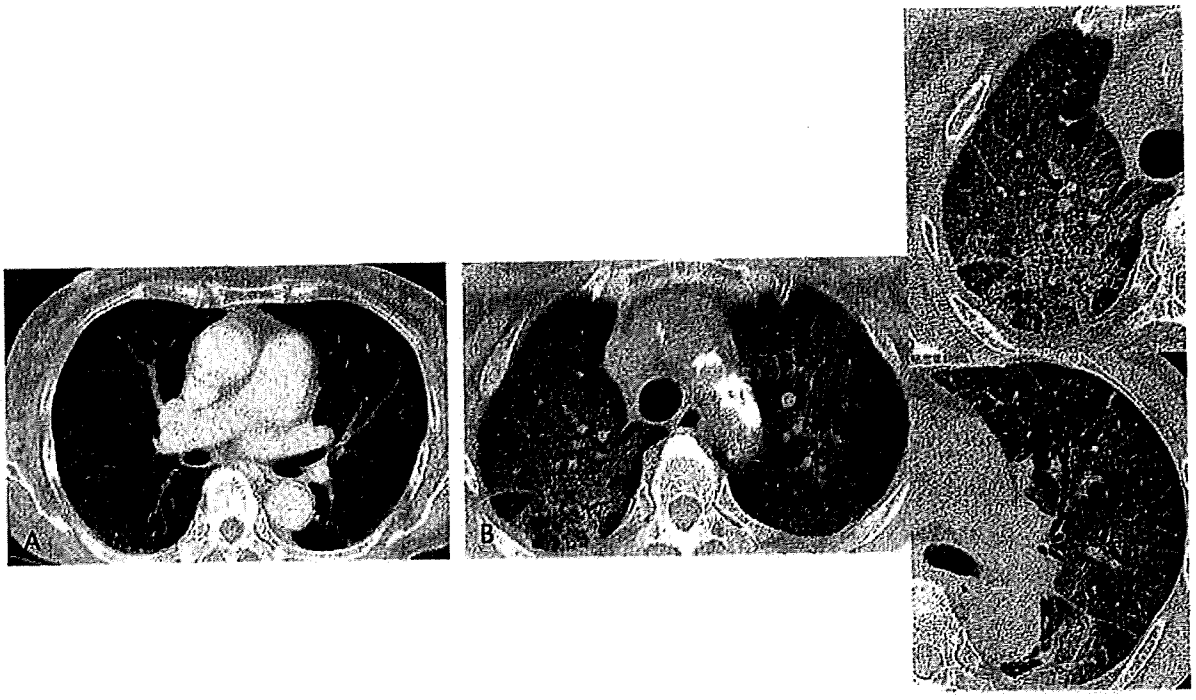


FIGURE 1. An example of CT imaging with severe pulmonary toxicity related to GEM. A, The CT imaging of patient number 8 before chemotherapy. B, The CT imagings of patient number 8 at appearance of severe pulmonary toxicity.

related to GEM were diffuse and bilateral ground glass opacity, thickened septal lines, reticular opacity, and no zonal predominance of lung opacity and no predilection or evidence of vascular engorgement and honeycombing. Furthermore, the most common CT pattern was that of acute interstitial pneumonia (seen in 6 of the 8 patients). We show the typical CT imaging of severe pulmonary toxicity related to GEM in Figure 1.

In all 9 patients, the percentage of oxygen saturation (%SpO_2) was under 90%, and all the patients required oxygen in a resting state. Furthermore, all the patients were regarded as having pulmonary toxicity and were treated with steroid pulse therapy.

Seven patients responded to steroid therapy and recovered. The remaining 2 did not respond and eventually died because of respiratory failure.

DISCUSSION

Gemcitabine is used to treat a variety of solid neoplasms. An analysis of 18 single-agent GEM studies comprising 790 patients concluded that GEM is a well-tolerated chemotherapeutic agent.[7] In this metaanalysis, pulmonary symptoms, most notably dyspnea, were reported in approximately 8% of the patients. These symptoms were typically mild and self-limiting.[7] However, life-threatening pulmonary toxicity has been described in rare case reports.[4–6] In an analysis of 22 single-agent GEM studies,[8] the incidence of grade 3 or 4 pulmonary toxicity was 1.4%. Furthermore, in the Research on Adverse Drug Events and Reports Pharmacovigilance program, which analyzed several studies and reports on the use of GEM,[9] the rate of GEM-associated lung injury was reported to be greater than 10%. In the present study, 9 (2.15%) of the 418 patients developed severe pulmonary toxicity possibly as a result of GEM, and 2 (11.76%) of the 15 patients treated with combination chemotherapy developed this complication. This result suggests that the incidence of severe pulmonary toxicity related to GEM after combination chemotherapy is higher than that after GEM alone. Furthermore, no differences in the incidences of this complication were observed when the patients were examined according to age, sex, history of smoking, and history of previous chemotherapy.

The median total dosage of GEM (11,000 mg/m^2) and the median onset of toxicity after the first administration of GEM (106 days) suggest that the incidence of severe pulmonary toxicity related to GEM will be generated in the capacity dependency. Gemcitabine administration is known to induce proinflammatory cytokines, and the extent to which TNF-α is released is known to be correlated with the pulmonary toxicity[10]; these phenomena may be related to the total dosage of GEM or the onset of toxicity.

The CT features of severe pulmonary toxicity related to GEM were identified as (1) diffuse ground glass opacification, (2) thickened septal lines, (3) reticular opacities, and (4) no cardiac enlargement or vascular engorgement, and these features were useful to exclude infection and lung edema.

All 9 patients were treated with steroid pulse therapy, and 2 patients died despite undergoing treatment with steroid therapy. This result showed that severe pulmonary toxicity related to GEM were potentially reversible in treatment with steroid.

CONCLUSIONS

The incidence of severe pulmonary toxicity related to GEM was rather low in the present study, but our findings suggested that the incidence might be higher after combination therapy. Pulmonary toxicity must be ruled out when patients exhibit respiratory difficulties. Acute interstitial pneumonia pattern was the most common CT feature pattern in patients with severe pulmonary toxicity related to GEM, and this complication is potentially reversible in treatment with steroid.

Akihiro Tamiya, MD
Department of Thoracic Oncology
Shizuoka Cancer Center
Shizuoka, Japan

Masahiro Endo, MD
Department of Diagnostic Radiology
Shizuoka Cancer Center
Shizuoka, Japan
m.endo@scchr.jp

Takehito Shukuya, MD

Satoshi Igawa, PhD

Asuka Tsuya, MD

Yukiko Nakamura, MD

Haruyasu Murakami, PhD

Toshiaki Takahashi, PhD
Department of Thoracic Oncology
Shizuoka Cancer Center
Shizuoka, Japan

Narikazu Boku, MD
Department of Gastrointestinal Oncology
Shizuoka Cancer Center
Shizuoka, Japan

Nobuyuki Yamamoto, MD
Department of Thoracic Oncology
Shizuoka Cancer Center
Shizuoka, Japan

REFERENCES

1. Heinemann V, Hertel LW, Grindey GB, et al. Comparison of the cellular pharmacokinetics and toxicity of 2′,2′-difluorodeoxycytidine and 1-beta-D-arabinofuranosylcytosine. *Cancer Res.* 1988;48:4024–4031.
2. Carmichael J, Fink U, Rusesell RCG, et al. Phase II study of gemcitabine in patients with advanced pancreatic cancer. *Br J Cancer.* 1996;73:101–105.
3. Okusaka T, Ishii H, Funakoshi A, et al. Phase II study of single-agent gemcitabine in patients with advanced biliary tract cancer. *Cancer Chemother Pharmacol.* 2006;57:647–653.
4. Pavlakis N, Bell DR, Millward MJ, et al. Fatal pulmonary toxicity resulting from treatment with gemcitabine. *Cancer.* 1997;82:1800–1801.
5. Attar EC, Ervin T, Janicek M, et al. Side effects of chemotherapy. Case 3. Acute interstitial pneumonitis related to gemcitabine. *J Clin Oncol.* 2000;18:697–698.
6. Ho Kim D, Shiozawa S, Tsuchiya A, et al. A case of drug-induced interstitial pneumonitis after adjuvant chemotherapy with gemcitabine for pancreatic cancer. *Gan To Kagaku Ryoho.* 2008;35:133–136.
7. Green MR. Gemcitabine safety overview. *Semin Oncol.* 1996;23:32–35.
8. Aapro MS, Martin C, Hatty S. Gemcitabine—a safety review. *Anticancer Drugs.* 1998;9:191–201.
9. Belknap SM, Kuzel TM, Yarnold PR, et al. Clinical features and correlates of gemcitabine-associated lung injury: finding from the RADAR project. *Cancer.* 2006;106:2051–2057.
10. LeVitt ML, Kassem B, Gooding WE, et al. Phase I study of gemcitabine given weekly as a short infusion for non-small cell lung cancer: results and possible immune system-related mechanisms. *Lung Cancer.* 2004;43:335–344.

Colonic Polyposis Associated With Autoimmune Pancreatitis

To the Editor:

Autoimmune pancreatitis (AIP) is now recognized as a pancreatic manifestation of immunoglobulin class G4 (IgG4)–associated autoimmune disorder with systemic involvement of the lung, biliary tract, kidney, lymph nodes, and salivary glands.[1] Because patients with this disease show both pancreatic and extrapancreatic lesions, it is possible that multiple types of antigens (Ags) are involved in its pathogenesis.[2,3] In this regard, a high incidence of inflammatory bowel diseases in AIP patients suggests that Ags derived from intestinal

Cancer Chemother Pharmacol (2009) 65:79–88
DOI 10.1007/s00280-009-1006-9

ORIGINAL ARTICLE

A dose-finding and pharmacokinetic study of nedaplatin in elderly patients with advanced non-small cell lung cancer

Noboru Yamamoto · Tomohide Tamura · Takayasu Kurata · Nobuyuki Yamamoto · Ikuo Sekine · Hideo Kunitoh · Yuichiro Ohe · Nagahiro Saijo

Received: 2 December 2008 / Accepted: 7 April 2009 / Published online: 26 April 2009

Abstract
Purpose Nedaplatin is a second-generation platinum showing favorable activity against non-small cell lung cancer (NSCLC). Dose-limiting toxicity (DLT) is thrombocytopenia, predicted by creatinine clearance (Ccr). This study was conducted to determine the recommended dose, and evaluate the toxicities, pharmacokinetics and efficacy for elderly NSCLC patients.
Methods Patients ≥70 years were stratified into two groups based on renal functions: Group A, Ccr ≥ 60 and Group B, 40 ≤ Ccr < 60. The initial doses were 80 and 60 mg/m^2 in Groups A and B, respectively. The doses were escalated in 20-mg/m^2 increments to 100 mg/m^2 until DLT.
Results Chemotherapy-naïve 39 elderly patients (Group A/Group B: 22/17) received a total of 83 cycles. Major toxicities were hematological. In Group A, one of the 15 patients at 100 mg/m^2 experienced DLT (neutropenia) and the recommended dose was determined at 100 mg/m^2. In Group B, three of the five patients had DLTs (leukopenia, neutropenia, thrombocytopenia and febrile neutropenia) at 100 mg/m^2, and the recommended dose was determined at 80 mg/m^2. The percentage decreases of neutrophil were well correlated with total and free-Pt AUCs. Partial responses were observed in 13 (33%) of the 39 patients, and 12 of the 13 patients who responded had a squamous cell carcinoma.
Conclusions Nedaplatin was administered simply and feasibly by stratifying renal function and exerted favorable antitumor activity for elderly patients with NSCLC, especially on squamous cell carcinoma.

Keywords Nedaplatin · Dose-finding study · Pharmacokinetics · NSCLC · Elderly patient

Presented in part at the 36th annual meeting of the American Society of Clinical Oncology, New Orleans, LA, 19–23 May 2000.

Noboru Yamamoto (✉) · T. Tamura · I. Sekine · H. Kunitoh · Y. Ohe
Division of Internal Medicine, National Cancer Center Hospital, 5-1-1, Tsukiji Chuo-ku, Tokyo 104-0045, Japan
e-mail: nbryamam@ncc.go.jp

T. Kurata
Cancer Chemotherapy Center, Osaka Medical College, Osaka, Japan

Nobuyuki Yamamoto
Division of Thoracic Oncology, Shizuoka Cancer Center Hospital, Shizuoka, Japan

N. Saijo
National Cancer Center Hospital East, Kashiwa, Japan

Introduction

The proportion of elderly patients with non-small cell lung cancer (NSCLC) is increasing [1]. At present, the first-line standard chemotherapy for non-elderly patients with advanced NSCLC is a platinum-based doublet regimen. The efficacy and feasibility of this strategy have been demonstrated in several randomized trials in patients with a good performance status and aged ≤70 years [2–4]. However, platinum-based doublet regimens are not always feasible for elderly patients. Age-related comorbidity and physiologic changes increase inter-individual pharmacokinetic variability, possibly leading to unacceptable severe toxicities. In particular, application of a cisplatin-based regimen to elderly patients is substantially restricted because of the risk of emesis, neurotoxicity and nephrotoxicity.

Oshita et al. [5] prospectively evaluated the feasibility of cisplatin-based chemotherapy in patients aged 75 years or older. Only 10 (29%) out of the 34 patients fulfilled the eligibility criteria for the cisplatin-based regimen. Furthermore, the majority of these eligible patients had grade 4 neutropenia and infectious episodes requiring antibiotics. In another analysis of cisplatin pharmacokinetics, the area under the plasma concentration versus time curve (AUC) of the ultrafilterable and total plasma platinum increased with age, and this was an independent predictor of cisplatin pharmacokinetics [6]. Therefore, the administration of cisplatin is restricted to highly select elderly patients.

(Glycolate-*O,O'*)-diammine platinum (II) (nedaplatin) is a second-generation platinum analog synthesized by Shionogi & Co., Ltd. (Osaka, Japan). In the preclinical studies, nedaplatin is highly active against solid tumors and has higher aqueous solubility than cisplatin [7–9]. The emesis and nephrotoxicity of nedaplatin are substantially reduced, compared with those of cisplatin, and multiple days of hydration for renal protection are not required [10]. Dose-limiting toxicity (DLT) is thrombocytopenia, and recommended dose in Japanese patient ≤70 years is 100 mg/m^2 every 4 weeks. This agent is active against NSCLC, with a response rate of 20.5% for previously untreated patients [10]. In a pharmacokinetic analysis, thrombocytopenia was significantly correlated with renal function (i.e., creatinine clearance [Ccr]), and nadir platelet count could be predicted from the following formula [11]:

$$[\text{Nadir platelet count}](/\text{mm}^3) = -64,264.7 + 2,783.4 \times [\text{Ccr}](\text{mL/min})$$

We conducted a dose-finding and pharmacokinetic study of nedaplatin in elderly patients with NSCLC, stratified into two groups based on renal function. This study was conducted to determine the recommended dose, and evaluate the toxicity profiles, pharmacokinetics and antitumor activity.

Patients and methods

Eligibility

Patients with histologically and cytologically confirmed chemotherapy-naïve advanced or metastatic non-small cell lung cancer were eligible for this study. Other eligibility criteria included the following: (1) age ≥70 years; (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (3) adequate bone marrow (white blood cell [WBC] count ≥4,000/mm^3, absolute neutrophil count [ANC] ≥2,000/mm^3, hemoglobin level ≥9.0 g/dL and platelet [PLT] count ≥100,000/mm^3), hepatic (serum total bilirubin level ≤1.5 mg/dL, serum asparatate aminotransferase [AST] level ≤100 IU/L and serum alanine aminotransferase [ALT] level ≤100 IU/L), renal (serum creatinine [Cr] level ≤1.5 mg/dL, creatinine clearance [Ccr] ≥40 mL/min) and pulmonary (PaO_2 ≥60 torr) functions.

The exclusion criteria were as follows: (1) symptomatic brain metastasis; (2) pleural or pericardial effusions and ascites requiring drainage; (3) serious pre-existing medical conditions such as uncontrolled infections, severe heart disease, uncontrolled diabetes and psychogenic disorders; and (4) hepatic B or C virus or human immunodeficiency virus infection.

Written informed consent was obtained from all the patients. This study was approved by the Institutional Review Board of the National Cancer Center.

Study design, dosage and dose escalation

This study was designed to determine the recommended dose of nedaplatin for elderly patients with advanced NSCLC, stratified into two groups based on renal function. The primary objective was to determine the recommended dose, and the secondary objectives were to evaluate toxicity profiles, pharmacokinetics and antitumor activity.

Patients were stratified into two groups based on their renal function at the time of study entry: Group A, Ccr ≥60 mL/min; and Group B, 40 ≤ Ccr < 60 mL/min. Ccr was measured on three consecutive days, and the mean value was used for stratification. Each Ccr was calculated using the following formula:

$$\text{Ccr}(\text{mL/min}) = [\text{urine volume}(\text{mL/min}) \times \text{urine creatinine}(\text{mg/dL})]/\text{serum creatinine}(\text{mg/dL})$$

In Group A, the initial dose of nedaplatin was 80 mg/m^2, and this was escalated to 100 mg/m^2. In Group B, the initial dose was 60 mg/m^2, and this was escalated to 80 and 100 mg/m^2. At least three to six patients were enrolled at each dose level, and the unacceptable dose was defined as the dose level at which >50% of the patients experienced DLT. The definition of DLT was as follows: (1) ≥grade 3 leukopenia, neutropenia or thrombocytopenia; (2) ≥grade 3 non-hematological toxicities except for alopecia, nausea and vomiting; (3) ≥grade 3 nausea and vomiting for ≥5 days. The recommended dose was defined as one dose level below the unacceptable dose level in each treatment arm.

Nedaplatin administration

Nedaplatin (Aqupla, (glycolate-*O,O'*)-diammine platinum (II); Shionogi Pharmaceutical Company, Osaka, Japan) was obtained commercially. Premedication, consisting of

3 mg of granisetron and 16 mg of dexamethasone diluted in 100 mL of 0.9% saline, was administered via a 30-minute intravenous (IV) infusion. The calculated doses of nedaplatin in both treatment groups were diluted in 300 mL of 0.9% saline and were administered using a 1-h IV infusion every 4 weeks. Following the nedaplatin administration, 500 mL of 0.9% saline was administered intravenously to provide minimal hydration.

Pretreatment and follow-up evaluation

On enrollment into the study, history and physical examination was performed. Complete differential blood cell count (including WBC count, ANC, hemoglobin and PLT), and clinical chemistry analysis (including serum total protein, albumin, bilirubin, Cr, AST, ALT, gamma-glutamyltransferase, and alkaline phosphatase) were performed. These above were performed at least twice a week throughout the study. Tumor measurement was planned every cycle, and antitumor response was assessed using the WHO standard response criteria. Toxicity was evaluated according to the National Cancer Institute common toxicity criteria (version 2.0).

PK study

Pharmacokinetic (PK) evaluations were performed in all patients during the initial cycle of treatment. Heparinized venous blood samples (7 mL) were taken before infusion, at 30 min and just before the end of infusion, as well as at 15 and 30 min and 1, 2, 3, 5, 7, 11, 23 and 47 h after the end of infusion.

Blood samples were centrifuged immediately at 4,000 rpm for 10 min. One milliliter of plasma was stored at −20°C or below in a polyethylene tube until the measurement of total plasma platinum (total-Pt) concentration. Residual plasma was transferred to an Amicon Centrifree tube (Amicon, Inc., Beverly, MA, USA) and centrifuged at 4,000 rpm for 20 min. Ultrafiltrate of the plasma was taken and stored at −20°C or below in a polyethylene tube until the measurement of the plasma-free platinum (free-Pt) concentration. The total-Pt and free-Pt concentrations were measured using flameless atomic absorption spectrometry, as previously reported [12].

The PK parameters were estimated using a nonlinear least-squares regression analysis (WinNonlin, Version 5.2; Bellkey Science, Inc., Chiba, Japan) with a weighting factor of $1/year^2$. The individual plasma concentration–time data were fitted to one-, two- and three-exponential equations using a zero-order infusion input and first-order elimination (corresponding to a one-, two- and three-compartment PK model). The model was chosen on the basis of Akaike's information criteria [13]. Fitted parameters (coefficients and exponent of exponential equations) were permitted in the computation of the following PK parameters: half life ($t_{1/2}$), area under the plasma concentration versus time curve (AUC), systemic clearance (CL), and volume of distribution at steady state (V_{dss}).

To assess the pharmacodynamic effect, percentage decrease was calculated in WBC, ANC or PLT according to the following formula:

$$\text{Percentage decrease} = [(\text{pretreatment count} - \text{nadir count})/(\text{pretreatment count})] \times 100.$$

These percentages were related to the AUC according to the sigmoid E_{max} model, as follows:

$$\text{Effect}(\%) = [E_{max}(\text{AUC})^k]/[\text{AUC}_{50}^k + \text{AUC}^k] \times 100.$$

A nonlinear least-squares regression using WinNonlin was used to estimate the AUC that produces 50% of the maximum effect (AUC_{50}) and the sigmoidicity coefficient (k).

Results

Patient characteristics

Between June 1996 and July 2001, 39 patients were stratified into two groups (22 in Group A and 17 in Group B) based on their renal functions at entry into the study (Table 1). They received a total of 83 cycles of therapy. The patients comprised 35 males and 4 females with good performance status, and the median age was 76 years in both treatment groups. All the patients were included in the toxicity evaluation. A total of 28 (72%) patients were included in the PK analysis and the remaining 11 (28%) were excluded because of insufficient PK samplings. Eight patients (two from Group A and six from Group B) had stage IIIA disease, but were not candidates for thoracic radiotherapy because of their poor pulmonary function. Six patients (five from Group A and one from Group B) received surgical resections for primary tumors. As much as 21 patients (54%, 12 from Group A and 9 from Group B) had squamous cell carcinoma. Nine patients (4 from Group A and 5 from Group B) received only one cycle of therapy because of progressive disease (PD) and 22 patients (12 from Group A and 10 from Group B) received two cycles of treatment. Among these 22 patients, partial response (PR), stable disease (SD) and PD were observed in 8, 10 and 4 patients, respectively. Five of eight patients with PR, two of ten with SD and one of four with PD received sequential thoracic radiotherapy for primary lesion following two cycles of treatment. Two of ten patients with SD and one of four with PD received palliative

radiotherapy for metastatic lesion. Two of four patients with PD received second-line chemotherapy. The remaining nine patients received supportive care according to the patients' request.

Toxicity

All the 39 patients were included in the toxicity evaluation. Major toxicities were hematological, such as leukopenia, neutropenia and thrombocytopenia, in both groups, and these hematological toxicities increased in severity with increased dose level of nedaplatin. In Group A, 1 (6.7%) out of the 15 patients treated at a dose level of 100 mg/m^2 had grade 3 neutropenia; this dose level was considered to be acceptable (Table 2). In Group B, three (50%) out of six patients treated at a dose level of 80 mg/m^2 had ≥grade 3 hematological toxicities (one with grade 3 neutropenia, another with grade 4 neutropenia and febrile neutropenia, and the other with grade 3 leukopenia, anemia and grade 4 thrombocytopenia). The patient with grade 4 thrombocytopenia required a platelet transfusion. At a dose level of 100 mg/m^2, three (60%) out of five patients had ≥grade 3 hematological toxicities (one with grade 3 leukopenia and neutropenia, another with grade 3 thrombocytopenia and grade 4 neutropenia, and the other with grade 3 leukopenia, thrombocytopenia and grade 4 neutropenia). These three patients had also febrile neutropenia. In Group B, a dose level of 100 mg/m^2 was considered to be unacceptable (Table 2).

Non-hematological toxicities, mainly nausea and anorexia, were generally mild in severity and were not dose limiting in either group (Table 3). Renal toxicity,

Table 1 Patient characteristics

	Group A (Ccr ≥60 mL/min)		Group B (40 ≤ Ccr < 60 mL/min)	
	No. of patients	Percentage	No. of patients	Percentage
Total patients enrolled	22	100	17	100
Assessable for toxicity	22	100	17	100
Assessable for PK analysis	15	68	13	76
Age, median (range), years	76 (70–82)		76 (70–78)	
Sex				
Male	19	86	16	94
Female	3	14	1	6
ECOG PS				
0	6	27	1	6
1	16	73	15	88
2	0	0	1	6
Stage				
IIIA	2	9	6	35
IIIB	4	18	6	35
IV	11	50	4	24
Postoperative recurrence	5	23	1	6
Pathological subtype				
Squamous cell carcinoma	12	54	9	53
Adenocarcinoma	9	41	8	47
P/D carcinoma	1	5	0	0
Dose of nedaplatin (mg/m^2)				
60	–	–	6	35
80	7	32	6	35
100	15	68	5	30
Treatment cycle				
Median (range)	2 (1–5)		2 (1–4)	
1 cycle	4	18	5	29
2 cycles	12	55	10	59
≥3 cycles	6	27	2	12

PK pharmacokinetics, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *P/D carcinoma* poorly differentiated carcinoma

Table 2 Hematological toxicity

Group A (Ccr ≥60 mL/min)	Dose level (mg/m^2), (number of patients)									
	80 (n = 7) Grade					100 (n = 15) Grade				
Event	0	1	2	3	4	0	1	2	3	4
Leukopenia	6	1	0	0	0	12	1	2	0	0
Neutropenia	6	1	0	0	0	8	4	2	1[a]	0
Anemia	4	2	1	0	0	5	7	3	0	0
Thrombocytopenia	7	0	0	0	0	12	2	1	0	0
No. of patients with febrile neutropenia	0					0				
No. of patients with DLT	0					1				

Group B (40 ≤ Ccr < 60 mL/min)	Dose level (mg/m^2), (number of patients)														
	60 (n = 6) Grade					80 (n = 6) Grade					100 (n = 5) Grade				
Event	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Leukopenia	5	1	0	0	0	2	1	2	1[a]	0	2	0	1	2[a]	0
Neutropenia	5	1	0	0	0	2	2	0	1[a]	1[a]	1	1	0	1[a]	2[a]
Anemia	4	1	1	0	0	3	1	1	1[a]	0	1	2	2	0	0
Thrombocytopenia	6	0	0	0	0	3	1	1	0	1[a]	2	1	0	2[a]	0
No. of patients with febrile neutropenia	0					1					3				
No. of patients with DLT	0					3					3				

[a] DLT

characterized as an increase in Cr, was also mild, and only one out of five patients treated at a dose level of 100 mg/m^2 in Group B had a grade 2 Cr increase. Considering the toxicity profiles, the recommended doses in Groups A and B were determined to be 100 and 80 mg/m^2, respectively.

Response and survival

The antitumor response was assessed in all the 39 patients (Table 4). Of the 39 patients who achieved PR, 13 had an overall response rate of 33%. Similar antitumor responses were observed in both treatment groups; that is, 6 (27%) of 22 and 7 (41%) of 17 patients had PRs in Groups A and B, respectively. Furthermore, 12 of the 13 patients with PRs in both groups had squamous cell carcinoma, and the response rate among patients with squamous cell carcinoma was 57%. Survival follow-up was completed in all the enrolled patients. The median survival time was 11.2 months (95% confidence interval: 7.7–14.6 months), and the 1-, 2- and 5-year survival rates were 46, 23 and 5%, respectively.

Pharmacokinetics

Pharmacokinetic analysis was performed using data from 28 (72%) of the 39 patients. The first patient enrollment in both treatment groups was started in 1996, and techniques of the sample centrifuging and measurement were not fully developed at the beginning of this pharmacokinetic study. Therefore, the remaining 11 patients (28%) were excluded for pharmacokinetic analysis. The mean plasma concentration–time profiles of total-Pt and free-Pt of nedaplatin are illustrated in Fig. 1. The plasma disappearances of total-Pt and free-Pt were biphasic, and the mean terminal half lives in all the assessable patients averaged 6.28 and 3.57 h, respectively. The C_{max} and AUC of the total-Pt and free-Pt tended to increase with the dose of nedaplatin. The AUCs of the total- and free-Pt at a dose of 100 mg/m^2 in Group A seemed similar to those at a dose of 80 mg/m^2 in Group B (Table 5), and there were no significant differences between these two treatment subgroups (P = 0.293 for total-Pt AUC and P = 0.336 for free-Pt AUC). Furthermore, the AUCs of free-Pt at the recommended doses in both groups (i.e., 100 mg/m^2 in Group A and 80 mg/m^2 in Group B) seemed also similar to that in patients aged 70 years or under who had been treated with 100 mg/m^2 of nedaplatin [14]. In the sigmoid Emax model assessing the pharmacodynamic effect of nedaplatin, the percentage decrease in the neutrophil counts were well correlated with the total-Pt (r = 0.652) and free-Pt (r = 0.723; Fig. 2).