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ORIGINAL REPORT

Randomized Pharmacokinetic and Pharmacodynamic Study of Docetaxel: Dosing Based on Body-Surface Area Compared With Individualized Dosing Based on Cytochrome P450 Activity Estimated Using a Urinary Metabolite of Exogenous Cortisol

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ABSTRACT

Purpose

Docetaxel is metabolized by cytochrome P450 (CYP3A4) enzyme, and the area under the concentration-time curve (AUC) is correlated with neutropenia. We developed a novel method for estimating the interpatient variability of CYP3A4 activity by the urinary metabolite of exogenous cortisol (6-beta-hydroxycortisol [6-β-OHF]). This study was designed to assess whether the application of our method to individualized dosing could decrease pharmacokinetic (PK) and pharmacodynamic (PD) variability compared with body-surface area (BSA) –based dosing.

Patients and Methods

Fifty-nine patients with advanced non–small-cell lung cancer were randomly assigned to either the BSA-based arm or individualized arm. In the BSA-based arm, 60 mg/m^2 of docetaxel was administered. In the individualized arm, individualized doses of docetaxel were calculated from the estimated clearance (estimated clearance = 31.177 + [7.655 × 10^{-4} × total 6-β-OHF] − [4.02 × alpha-1 acid glycoprotein] − [0.172 × AST] − [0.125 × age]) and the target AUC of 2.66 mg/L · h.

Results

In the individualized arm, individualized doses of docetaxel ranged from 37.4 to 76.4 mg/m^2 (mean, 58.1 mg/m^2). The mean AUC and standard deviation (SD) were 2.71 (range, 2.02 to 3.40 mg/L · h) and 0.40 mg/L · h in the BSA-based arm, and 2.64 (range, 2.15 to 3.07 mg/L · h) and 0.22 mg/L · h in the individualized arm, respectively. The SD of the AUC was significantly smaller in the individualized arm than in the BSA-based arm ($P < .01$). The percentage decrease in absolute neutrophil count (ANC) averaged 87.1% (range, 59.0 to 97.7%; SD, 8.7) in the BSA-based arm, and 87.4% (range, 78.0 to 97.2%; SD, 6.1) in the individualized arm, suggesting that the interpatient variability in percent decrease in ANC was slightly smaller in the individualized arm.

Conclusion

The individualized dosing method based on the total amount of urinary 6-β-OHF after cortisol administration can decrease PK variability of docetaxel.

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INTRODUCTION

Many cytotoxic drugs have narrow therapeutic windows despite having a large interpatient pharmacokinetic (PK) variability. The doses of these cytotoxic drugs are usually calculated on the basis of body-surface area (BSA). Although several physiologic functions are proportional to BSA, systemic exposure to a drug is only partially related to

this parameter.[1-3] Consequently, a large interpatient PK variability is seen when doses are based on BSA. This large interpatient PK variability can result in undertreatment with inappropriate therapeutic effects in some patients, or in overtreatment with unacceptable severe toxicities in others. Understanding interpatient PK variability is important for optimizing anticancer treatments. Factors that affect PK variability include drug absorption, metabolism, and excretion. Among these factors, drug metabolism is regarded as a major factor causing PK variability. Unfortunately, however, no simple and practical method for estimating the interpatient variability of drug metabolism is available. If drug metabolism in each patient could be predicted, individualized dosing could be performed to optimize drug exposure while minimizing unacceptable toxicity.

Docetaxel is a cytotoxic agent that promotes microtubule assembly and inhibits depolymerization to free tubulin, resulting in the blockage of the M phase of the cell cycle.[4] Docetaxel has shown promising activity against several malignancies, including non–small-cell lung cancer, and is metabolized by hepatic CYP3A4 enzyme.[5-15]

Human CYP3A4 is a major cytochrome P450 enzyme that is present abundantly in human liver microsomes and is involved in the metabolism of a large number of drugs, including anticancer drugs.[16-18] This enzyme exhibits a remarkable interpatient variation in activity as high as 20-fold, which accounts for the large interpatient differences in the disposition of drugs that are metabolized by this enzyme.[19-22] Several noninvasive in vivo probes for estimating the interpatient variability of CYP3A4 activity have been reported and include the erythromycin breath test, the urinary dapsone recovery test, measurement of midazolam clearance (CL), and measurement of the ratio of endogenous urinary 6-beta-hydroxycortisol (6-β-OHF) to free-cortisol (FC).[23-27] The erythromycin breath test and the measurement of midazolam CL are the best validated, and both have been shown to predict docetaxel CL in patients.[28,29] However, neither probe has been used in a prospective study to validate the correlations observed, or to test their utility in guiding individualized dosing.

We developed a novel method for estimating the interpatient variability of CYP3A4 activity by urinary metabolite of exogenous cortisol. The total amount of 24-hour urinary 6-β-OHF after cortisol administration (total 6-β-OHF) is significantly correlated with docetaxel CL, which is metabolized by the CYP3A4 enzyme. We also illustrate the possibility that individualized dosing to optimize drug exposure and decrease interpatient PK variability could be performed using this method.[30]

We conducted a prospective, randomized PK and pharmacodynamic (PD) study of docetaxel comparing BSA-based dosing and individualized dosing based on the interpatient variability of CYP3A4 activity, as estimated by a urinary metabolite of exogenous cortisol. The objective of this study was to assess whether the application of our method to individualized dosing could decrease PK and PD variability of docetaxel compared with BSA-based dosing.

PATIENTS AND METHODS

Patient Selection

Patients with histologically or cytologically documented advanced or metastatic non–small-cell lung cancer were eligible for this study. Other eligibility criteria included the following: age $\geq$ 20 years; Eastern Cooperative Oncology Group performance status of 0, 1, or 2; 4 weeks of rest since any previous anticancer therapy; and adequate bone marrow (absolute neutrophil count [ANC] $\geq$ 2,000/μL and platelet count $\geq$ 100,000/μL), renal (serum creatinine level $\leq$ 1.5 mg/dL), and hepatic (serum total bilirubin level $\leq$ 1.5 mg/dL, AST level $\leq$ 150 U/L, and ALT level $\leq$ 150 U/L) function. Written informed consent was obtained from all patients before enrollment onto the study.

The exclusion criteria included the following: pregnancy or lactation; concomitant radiotherapy for primary or metastatic sites; concomitant chemotherapy with any other anticancer agents; treatment with steroids or any other drugs known to induce or inhibit CYP3A4 enzyme[17]; serious pre-existing medical conditions, such as uncontrolled infections, severe heart disease, diabetes, or pleural or pericardial effusions requiring drainage; and a known history of hypersensitivity to polysorbate 80. This study was approved by the institutional review board of the National Cancer Center.

Pretreatment and Follow-Up Evaluation

On enrollment onto the study, a history and physical examination were performed, and a complete differential blood cell count (including WBC count, ANC, hemoglobin, and platelets), and a clinical chemistry analysis (including serum total protein, albumin [ALB], bilirubin, creatinine, AST, ALT, gamma-glutamyltransferase, alkaline phosphatase [ALP], and alpha-1 acid glycoprotein [AAG]) were performed. Blood cell counts and a chemistry analysis except for AAG were performed at least twice a week throughout the study. Tumor measurements were performed every two cycles, and antitumor response was assessed by WHO standard response criteria. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

Study Design

This study was designed to assess whether the application of our method to individualized dosing could decrease PK and PD variability compared with BSA-based dosing. The primary end point was PK variability and the secondary end point was PD variability (ie, toxicity). In our previous study involving 29 patients who received 60 mg/m^2 of docetaxel, the area under the concentration-time curve (AUC) was calculated to be 2.66 $\pm$ 0.91 (mean $\pm$ standard deviation [SD]) mg/L $\cdot$ h.[30] We assumed that the variability of AUC, represented by the SD, could be reduced by 50% in the individualized arm compared with that in the BSA-based arm, and that AUC would be normally distributed. The required sample size was 25 patients per arm to detect this difference with a two-sided F test at $\alpha = .05$ and a power of 0.914.

Patients were randomly assigned to either the BSA-based arm or individualized arm (Fig 1). In the BSA-based arm, each patient received a dose of 60 mg/m^2 of docetaxel. In the individualized arm, individualized doses of docetaxel were calculated from the estimated docetaxel CL after cortisol administration and the target AUC (described in the Docetaxel Administration section).

Cortisol Administration and Urine Collection

In the individualized arm, 300 mg of hydrocortisone (Banyu Pharmaceuticals Co, Tokyo, Japan) was diluted in 100 mL of 0.9%

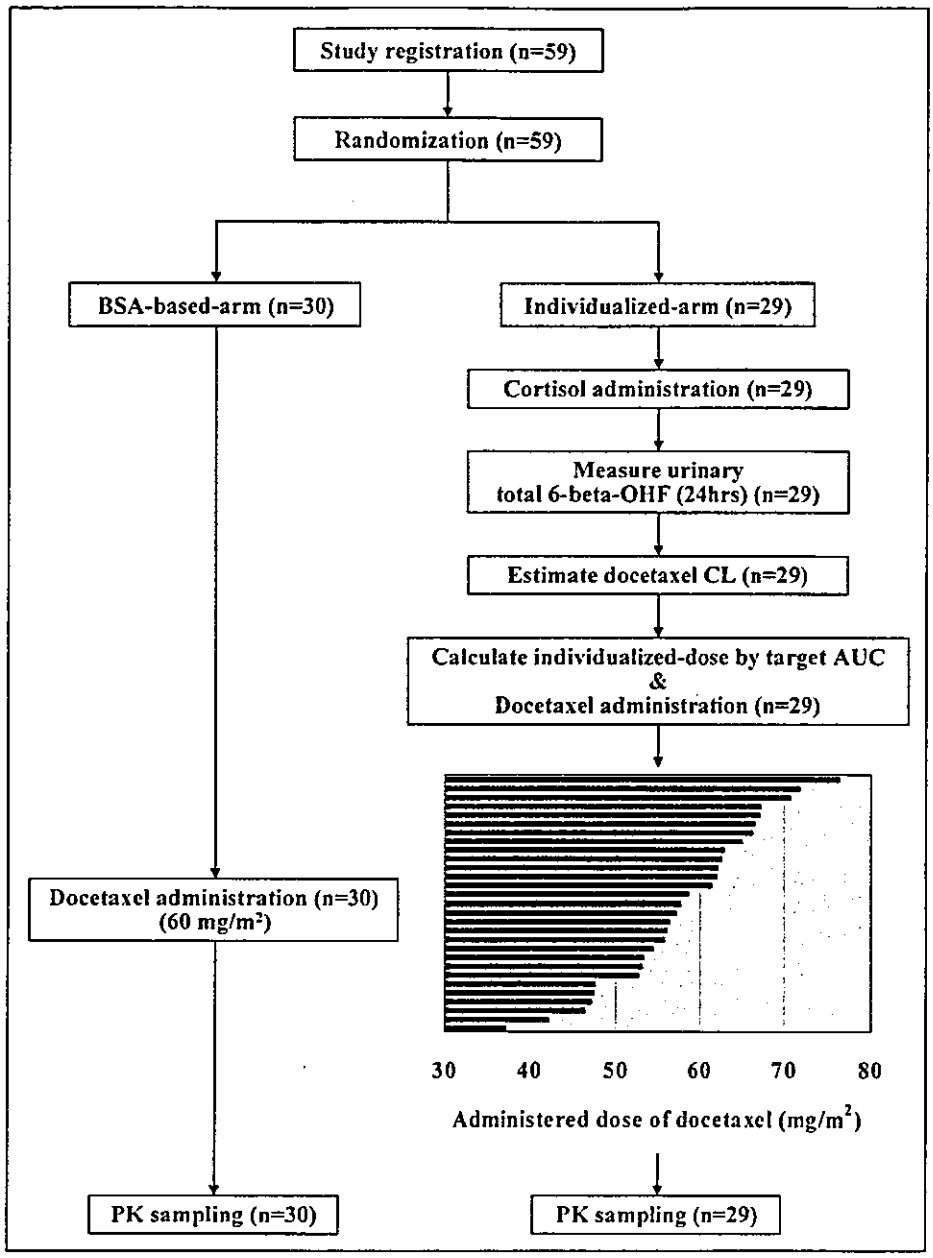

Fig 1. Study flow diagram and administered dose of docetaxel. PK, pharmacokinetic; AUC, area under the concentration-time curve; CL, clearance; 6-β-OHF, 6-beta-hydroxycortisol.

saline and administered intravenously for 30 minutes at 9 AM on day 1 in all patients to estimate the interpatient variability of CYP3A4 activity. After cortisol administration, the urine was collected for 24 hours. The total volume of the 24-hour collection was recorded, and a 5-mL aliquot was analyzed immediately.

Docetaxel Administration

Docetaxel (Taxotere; Aventis Pharm Ltd, Tokyo, Japan) was obtained commercially as a concentrated sterile solution containing 80 mg of the drug in 2 mL of polysorbate 80. In the BSA-based arm, a dose of 60 mg/m^2 of docetaxel was diluted in 250 mL of 5% glucose or 0.9% saline and administered by 1-hour intravenous infusion at 9 AM to all patients.

In the individualized arm, individualized dose of docetaxel was calculated from the estimated CL and the target AUC of 2.66 mg/L · h using the following equations:

$$\text{Estimated CL (L/h/m}^2) = 31.177 + (7.655 \times 10^{-4} \times \text{total-6-}\beta\text{-OHF [}\mu\text{g/d]}) - (4.02 \times \text{AAG [g/L]}) - (0.172 \times \text{AST [U/L]}) - (0.125 \times \text{age [years]})^{30}$$

$$\text{Individualized dose of docetaxel (mg/m}^2) = \text{estimated docetaxel CL (L/h/m}^2) \times \text{target AUC (2.66 mg/L} \cdot \text{h)}$$

At least 2 days after cortisol administration, individualized doses of docetaxel were diluted in 250 mL of 5% glucose or 0.9% saline and administered by 1-hour intravenous infusion at 9 AM to each patient. The doses of docetaxel in subsequent cycles of treatment were unchanged, and no prophylactic premedication to protect against docetaxel-related hypersensitivity reactions was administered in either of the treatment arms.

PK Study

Blood samples for PK studies were obtained from all of the patients during the initial treatment cycle. An indwelling cannula was inserted in the arm opposite that used for the drug infusion, and blood samples were collected into heparinized tubes. Blood samples were collected before the infusion; 30 minutes after the start of the infusion; at the end of the infusion; and 15, 30, and 60 minutes and 3, 5, 9, and 24 hours after the end of the infusion. All blood samples were centrifuged immediately at 4,000 rpm for 10 minutes, after which the plasma was removed and the samples were placed in polypropylene tubes, labeled, and stored at −20°C or colder until analysis.

PK parameters were estimated by the nonlinear least squares regression analysis method (WinNonlin, Version 1.5; Bellkey Science Inc, Chiba, Japan) with a weighting factor of 1 per year.[2] Individual plasma concentration-time data were fitted to two- and three-compartment PK models using a zero-order infusion input and first-order elimination. The model was chosen on the basis of Akaike's information criteria.[31] The peak plasma concentration (C_{max}) was generated directly from the experimental data. AUC was extrapolated to infinity and determined based on the best-fitted curve; this measurement was then used to calculate the absolute CL (L/h), defined as the ratio of the delivered dosage (in milligrams) and AUC.

To assess PD effect of docetaxel, the percentage decrease in ANC was calculated according to the following formula: % decrease in ANC = (pretreatment ANC − nadir ANC)/(pretreatment ANC) × 100.

Measurements

The concentration of urinary 6-β-OHF was measured by reversed phase high-performance liquid chromatography with UV absorbance detection according to previously published methods.[30,32,33]

Docetaxel concentrations in plasma were also measured by solid-phase extraction and reversed phase high-performance liquid chromatography with UV detection according to the previously published method.[30,34] The detection limit corresponded to a concentration of 10 ng/mL.

Statistical Analysis

Fisher's exact test or χ^2 test was used to compare categoric data, and Student's t test was used for continuous variables. The strength of the relationship between the estimated docetaxel CL and the observed docetaxel CL was assessed by least squares linear regression analysis. The interpatient variability of AUC for each arm was evaluated by determining the SD and was compared by F test. Biases, or the mean AUC value in each arm minus the target AUC (2.66 mg/L · h), were also compared between the arms by Student's t test.

A two-sided P value of ≤ .05 or less was considered to indicate statistical significance. All statistical analyses were performed using SAS software version 8.02 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Between October 1999 and May 2001, 59 patients were enrolled onto the study and randomly assigned to either the BSA-based arm (n = 30) or the individualized arm (n = 29). All 59 patients were assessable for PK and PD analyses. The pretreatment characteristics of the 59 patients are listed in Table 1. The baseline characteristics were well balanced between the arms except for three laboratory parameters: ALB, AAG, and ALP. These three parameters were not included in the eligibility criteria. The majority of patients (95%) had a performance status of 0 or 1. Twenty (67%) and 16 (55%) patients had been treated with platinum-based chemotherapy in the BSA-based arm and individualized arm, respectively. Only two patients in the individualized arm had liver metastasis, and most of the patients had good hepatic functions.

Individualized Dosing of Docetaxel

In the individualized arm, the total amount of 24-hour urinary 6-β-OHF after cortisol administration (total 6-β-OHF) was 9,179.6 ± 3,057.7 μg/d (mean ± SD), which was similar to the result of our previous study.[30] The estimated docetaxel CL was 21.9 ± 3.5 L/h/m^2 (mean ± SD), and individualized dose of docetaxel ranged from 37.4 to 76.4 mg/m^2 (mean, 58.1 mg/m^2; Fig 1).

PK

Docetaxel PK data were obtained from all 59 patients during the first cycle of therapy, and PK parameters are listed in Table 2. Drug levels declined rapidly after infusion and could be determined to a maximum of 25 hours. The concentration of docetaxel in plasma was fitted to a biexponential equation, which was consistent with previous reports.[30,35-38] The mean alpha and beta half-lives were 9.2 minutes and 5.0 hours in the BSA-based arm and 9.2 minutes and 7.4 hours in the individualized arm, respectively.

In the BSA-based arm, docetaxel CL was 22.6 ± 3.4 L/h/m^2 (mean ± SD), and AUC averaged 2.71 mg/L · h (range, 2.02 to 3.40 mg/L · h). In the individualized arm, docetaxel CL was 22.1 ± 3.4 L/h/m^2, and AUC averaged 2.64 mg/L · h (range, 2.15 to 3.07 mg/L · h). The least squares linear regression analysis showed that the observed docetaxel CL was well estimated in the individualized arm (r^2 = 0.821; Fig 2).

The SDs of AUC in the BSA-based arm and in the individualized arm were 0.40 and 0.22, respectively, and the ratio of SD in the individualized arm to that in the BSA-based arm was 0.538 (95% CI, 0.369 to 0.782). The biases from the target AUC in the BSA-based arm and in the individualized arm were 0.047 (95% CI, −0.104 to 0.198) and −0.019 (95% CI, −0.102 to 0.064), respectively, with no significant difference. The interpatient variability of

Table 1. Patient Characteristics

Characteristic	BSA-Based Arm No. of Patients	%	Individualized Arm No. of Patients	%	P
Enrolled	30		29		
Eligible	30	100	29	100	
Age, years					.62
Median	61		62		
Range	52-73		45-73		
Sex					
Male	25	83	19	66	.14
Female	5	17	10	34	
ECOG PS					
0	7	23	1	3	.08
1	22	73	26	90	
2	1	3	2	7	
Prior treatment					
None	4	13	4	14	.99
Surgery	11	37	9	31	.65
Radiotherapy	13	43	10	34	.49
Chemotherapy	21	70	18	62	.52
Platinum-based regimens	20	67	16	55	.37
Site of disease					
Lung	23	77	28	97	.10
Liver	0	0	2	7	.24
Pleura	8	27	12	41	.23
Bone	7	23	9	31	.71
Extrathoracic lymph nodes	0	33	10	34	.93
Laboratory parameters					
ALB, g/L					.02
Median	38		35		
Range	26-45		24-44		
AAG, g/L					.04
Median	1.00		1.25		
Range	0.28-2.15		0.64-2.54		
AST, U/L					.67
Median	21		22		
Range	10-40		7-41		
ALT, U/L					.88
Median	18		18		
Range	6-54		4-45		
ALP, U/L					.03
Median	249		324		
Range	129-540		185-986		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status, ALB, serum albumin; AAG, alpha-1-acid glycoprotein; ALP, serum alkaline phosphatase.

AUC was significantly smaller in the individualized arm than in the BSA-based arm ($P < .01$; Fig 3).

PD

In both arms, neutropenia was the predominant toxicity related to docetaxel treatment, and 28 of 30 (93%) patients in the BSA-based arm and 25 of 29 (86%) patients in the individualized arm had grade 3 or 4 neutropenia.

Table 2. Docetaxel PK Parameters

Parameters	BSA-Based Arm (n = 30)	Individualized Arm (n = 29)
C_{max}, μg/mL	0.36-2.70	0.99-2.41
$t_{1/2}$ alpha*, minutes	9.2 ± 3.3	9.2 ± 2.7
$t_{1/2}$ beta*, hours	5.0 ± 4.8	7.4 ± 11.7
CL* L/h	37.6 ± 6.3	34.8 ± 7.1
CL* L/h/m²	22.6 ± 3.4	22.1 ± 3.4
AUC		
Mean mg/L · h	2.71	2.64
Range mg/L · h	2.02-3.40	2.15-3.07
Median	2.65	2.66
SD	0.40	0.22

Abbreviations: PK, pharmacokinetic; BSA, body-surface area; CL, clearance; AUC, area under concentration-time curve; SD, standard deviation.
*Data represent mean ± SD.

Nonhematologic toxicities, such as gastrointestinal and hepatic toxicities (ie, hyperbilirubinemia, aminotransferase elevations), were mild in both arms.

PD effects shown as the percentage decrease in ANC are listed in Table 3. The percentage decrease in ANC for the BSA-based arm and individualized arm were 87.1% (range, 59.0 to 97.7%; SD, 8.7) and 87.5% (range, 78.0 to 97.2%; SD, 6.1), respectively, suggesting that the interpatient variability in the percentage decrease in ANC was slightly smaller in the individualized arm than in the BSA-based arm (Fig 4). The response rates between the two arms were similar; five of 30 (16.7%) and four of 29 (13.8%) patients

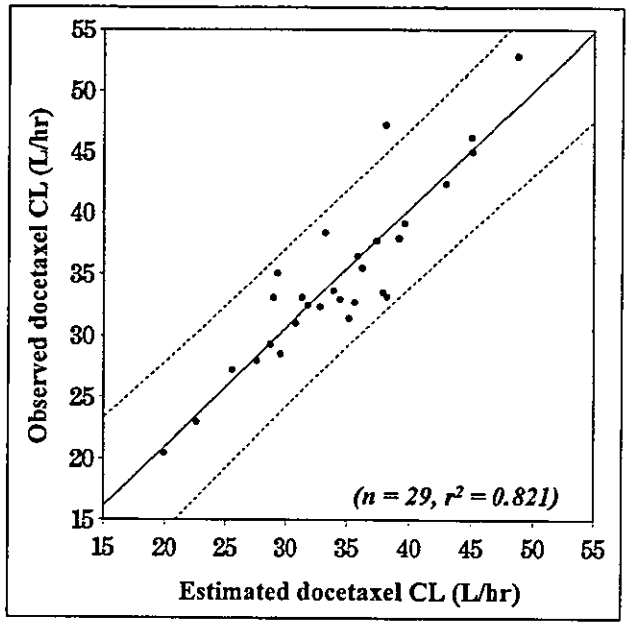

Fig 2. Correlation between the estimated and observed docetaxel clearance (CL) in the individualized arm (n = 29). (—) Linear regression line (r^2 = 0.821); (- - - -) 95% CIs for individual estimates.

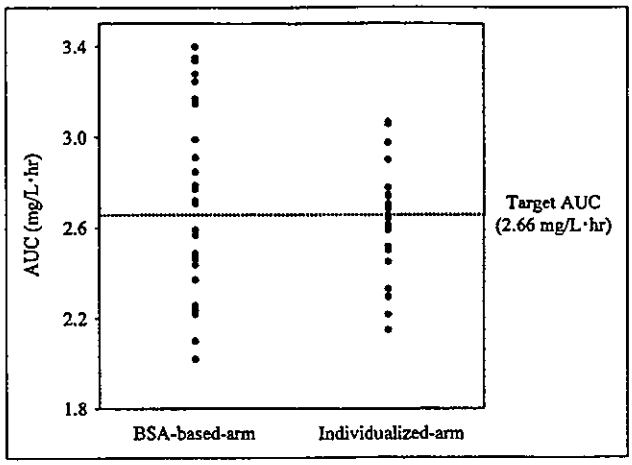

Fig 3. Comparison of area under the concentration-time curve (AUC) variability between the arms ($P < .01$; F test). BSA, body-surface area.

achieved a partial response in the BSA-based arm and individualized arm, respectively.

DISCUSSION

In oncology practice, the prescribed dose of most anticancer drugs is currently calculated from BSA of individual patients to reduce the interpatient variability of drug exposure. However, PK parameters, such as CL of many anticancer drugs, are not related to BSA.[2,39-43] Although PK parameters of docetaxel are correlated with BSA, individualized dosing based on individual metabolic capacities could further decrease the interpatient variability.[43]

CYP3A4 plays an important role in the metabolism of many drugs, including anticancer agents such as docetaxel, paclitaxel, vinorelbine, and gefitinib. This enzyme exhibits a large interpatient variability in metabolic activity, accounting for the large interpatient PK and PD variability. We have developed a novel method of estimating the interpatient variability of CYP3A4 activity by urinary metabolite of exogenous cortisol. That is, the total amount of 24-hour urinary 6-β-OHF after cortisol administration was highly correlated with docetaxel CL. We conducted a prospective randomized PK and PD study of docetaxel to evaluate whether the application of our method to individualized dosing could decrease PK and PD variability compared with BSA-based dosing.

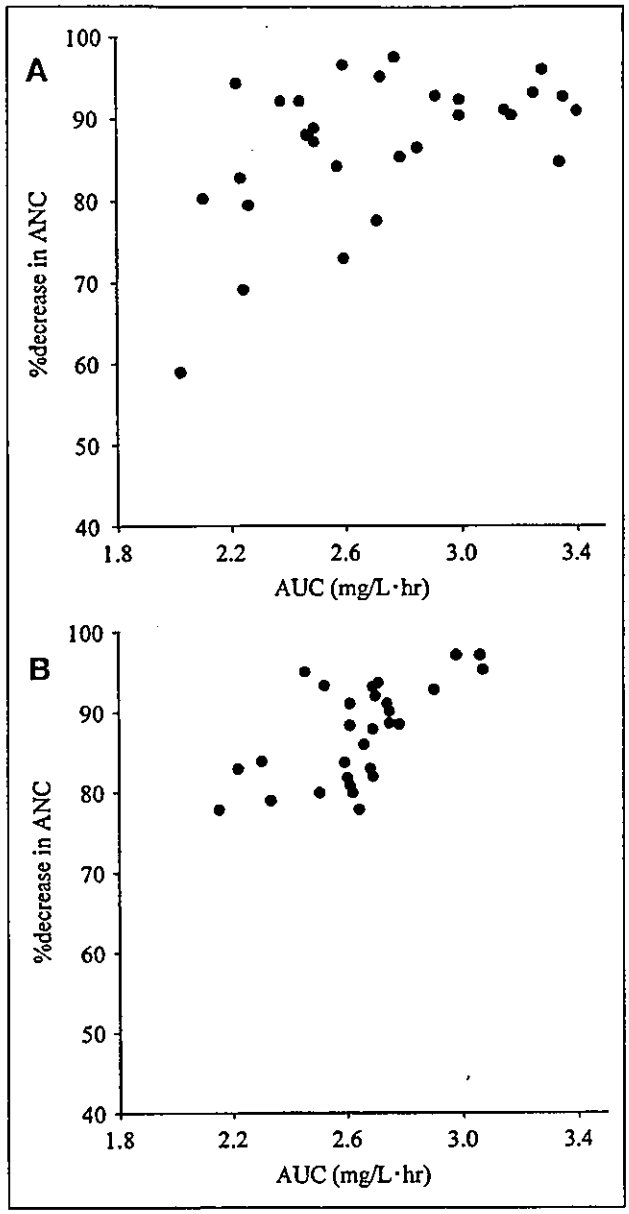

Fig 4. Correlation between area under the concentration-time curve (AUC) and percentage decrease in absolute neutrophil count (ANC) in each arm. (A) body-surface area–based arm; (B) individualized arm.

Table 3. Percentage Decrease in ANC

Parameters	BSA-Based Arm (n = 30)	Individualized Arm (n = 29)
Percentage decrease in ANC, %		
Mean	87.1	87.4
Range	59.0-97.7	78.0-97.2
Median	89.7	88.4
SD	8.7	8.1

Abbreviations: ANC, absolute neutrophil count; BSA, body-surface area; SD, standard deviation.

The study by Hirth et al[28] showed a good correlation between the result of the erythromycin breath test and docetaxel CL, and the study by Goh et al[29] showed a good correlation between the midazolam CL and docetaxel CL. In our study, we prospectively validated the correlation between docetaxel CL and our previously published method using the total amount of urinary 6-β-OHF after

cortisol administration in the individualized arm. As shown in Fig 2, the observed docetaxel CL was well estimated, and the equation for the estimation of docetaxel CL developed in our previous study was found to be reliable and reproducible. The target AUC in the individualized arm was set at 2.66 mg/L · h. This value was the mean value from our previous study, in which 29 patients were treated with 60 mg/m^2 of docetaxel. Individualized doses of docetaxel ranged from 37.4 to 76.4 mg/m^2 and were lower than expected.

The SD of AUC in the individualized arm was about 46.2% smaller than that in the BSA-based arm, a significant difference; this result seems to indicate that the application of our method to individualized dosing can reduce the interpatient PK variability. Assuming that the variability of AUC could be decreased 46.2% by individualized dosing applying our method, overtreatment could be avoided in 14.5% of BSA-dosed patients by using individualized dosing (Fig 5, area A), and undertreatment could be avoided in another 14.5% of these patients (Fig 5, area B). We considered that neutropenia could be decreased with patients in area A by individualized dosing. However, it is unknown whether the therapeutic effect of docetaxel could be improved in the patients in area B by individualized dosing because no significant positive correlation has been found between docetaxel AUC and antitumor response in patients with non–small-cell lung cancer.[43] In this study, seven of 30 (23.3%) and two of 30 (6.7%) patients in the BSA-based arm were included in area A and B, respectively (Figs 3 and 5).

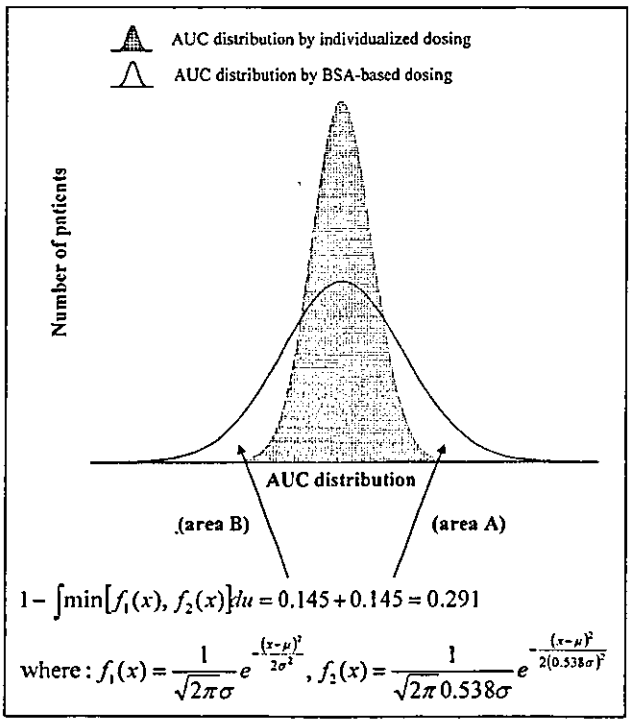

Fig 5. Simulated comparison of area under the concentration-time curve (AUC) distribution between body-surface area (BSA) –based dosing and individualized dosing when the variability of AUC is decreased 46.2% by individualized dosing applied using our method.

As shown in Figure 4, the percentage decrease in ANC was well correlated with AUC in both arms, which was similar to previous reports.[37,43] It was also indicated that the interpatient variability in the percentage decrease in ANC was slightly smaller in the individualized arm than in the BSA-based arm; however, this difference was not significant. The response rates between the two arms were similar. Although the interpatient PK variability could be decreased by individualized dosing in accordance with our method, the interpatient PD variability such as toxicity and the antitumor response could not be decreased. Several reasons could be considered.

With regard to toxicity, the pretreatment characteristics of the patients in this study were highly variable. More than half of the patients in each arm had previously received platinum-based chemotherapy, and more than 30% had received radiotherapy. The laboratory parameters (ie, ALB, AAG, and ALP) were not balanced across the arms, although they were not included in the eligibility criteria (Table 1). These variable pretreatment characteristics and unbalanced laboratory parameters may have influenced the frequency and severity of the hematologic toxicity as well as the pharmacokinetic profiles. The antitumor effect may have been influenced by the intrinsic sensitivity of tumors, the variable pretreatment characteristics, and the imbalance in laboratory parameters. Non–small-cell lung cancer is a chemotherapy-resistant tumor. The response rate for docetaxel ranges from 18% to 38%,[5] and no significant positive correlation between docetaxel AUC and antitumor response has been found. We considered it quite difficult to control the interpatient PD variability by controlling the interpatient PK variability alone. Although we did not observe any outliers in either arm, such as the two outliers with severe toxicity observed in the study by Hirth et al,[28] our method may be more useful for identifying such outliers. If we had not excluded patients with more abnormal liver function or a history of liver disease by the strict eligibility criteria, the results with the two dosing regimens may have been more different, and the interpatient PD variability, such as the percentage decrease in ANC, may have been smaller in the individualized arm than in the BSA-based arm. Furthermore, the primary end point of this study was PK variability, evaluated by the SD of AUC in both arms, and the sample size was significantly underpowered to evaluate whether the application of our method to individualized dosing could decrease PD variability compared with BSA-based dosing.

For the genotypes of CYP3A4, several genetic polymorphisms have been reported (http://www.imm.ki.se/CYPalleles/); however, a clear relationship between genetic polymorphisms and the enzyme activity of CYP3A4 has not been reported. Our phenotype-based

individualized dosing using the total amount of urinary 6-β-OHF after cortisol administration produced good results. However, this method is somewhat complicated, and a simpler method would be of great use. We analyzed the expression of CYP3A4 mRNA in the peripheral-blood mononuclear cells of the 29 patients in the individualized arm. No correlation was observed between the expression level of CYP3A4 mRNA and docetaxel CL or the total amount of urinary 6-β-OHF after cortisol administration (data not shown).

In conclusion, the individualized dosing of docetaxel using the total amount of urinary 6-β-OHF after cortisol administration is useful for decreasing the interpatient PK variability compared with the conventional BSA-based method of dosing. This method may be useful for individualized chemotherapy.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Sawyer M, Ratain MJ: Body surface area as a determinant of pharmacokinetics and drug dosing. Invest New Drugs 19:171-177, 2001
2. Gurney H: Dose calculation of anticancer drugs: A review of the current practice and introduction of an alternative. J Clin Oncol 14: 2590-2611, 1996
3. Ratain MJ: Body-surface area as a basis for dosing of anticancer agents: Science, myth, or habit? J Clin Oncol 16:2297-2298, 1998
4. Ringel I, Horwitz SB: Studies with RP 56976 (Taxotere): A semisynthetic analogue of taxol. J Natl Cancer Inst 83:288-291, 1991
5. Cortes JE, Pazdur R: Docetaxel. J Clin Oncol 13:2643-2655, 1995
6. Fossella FV, Lee JS, Murphy WK, et al: Phase II study of docetaxel for recurrent or metastatic non-small-cell lung cancer. J Clin Oncol 12:1238-1244, 1994
7. Fossella FV, Lee JS, Shin DM, et al: Phase II study of docetaxel for advanced or metastatic platinum-refractory non-small-cell lung cancer. J Clin Oncol 13:645-651, 1995
8. Gandara DR, Vokes E, Green M, et al: Activity of docetaxel in platinum-treated non-small-cell lung cancer: Results of a phase II multicenter trial. J Clin Oncol 18:131-135, 2000
9. Kunitoh H, Watanabe K, Onoshi T, et al: Phase II trial of docetaxel in previously untreated advanced non-small-cell lung cancer: A Japanese cooperative study. J Clin Oncol 14:1649-1655, 1996
10. Fossella FV, DeVore R, Kerr RN, et al: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens: The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 18:2354-2362, 2000
11. Shepherd FA, Dancey J, Ramlau R, et al: Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095-2103, 2000
12. Hudis CA, Seidman AD, Crown JP, et al: Phase II and pharmacologic study of docetaxel as initial chemotherapy for metastatic breast cancer. J Clin Oncol 14:58-65, 1996
13. Trudeau ME, Eisenhauer EA, Higgins BP, et al: Docetaxel in patients with metastatic breast cancer: A phase II study of the National Cancer Institute of Canada-Clinical Trials Group. J Clin Oncol 14:422-428, 1996
14. Chan S, Friedrichs K, Noel D, et al: Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer: The 303 Study Group. J Clin Oncol 17:2341-2354, 1999
15. Marre F, Sanderink GJ, de Sousa G, et al: Hepatic biotransformation of docetaxel (Taxotere) *in vitro*: Involvement of the CYP3A subfamily in humans. Cancer Res 56:1296-1302, 1996
16. Nelson DR, Koymans L, Kamataki T, et al: P450 superfamily: Update on new sequences, gene mapping, accession numbers and nomenclature. Pharmacogenetics 6:1-42, 1996
17. Lin JH, Lu AYH: Inhibition and induction of cytochrome P450 and the clinical implications. Clin Pharmacokinet 35:361-390, 1998
18. Parkinson A: An overview of current cytochrome P450 technology for assessing the safety and efficacy of new materials. Toxicol Pathol 24:45-57, 1996
19. Shimada T, Yamazaki H, Mimura M, et al: Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: Studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther 270:414-423, 1994
20. Guengerich FP: Characterization of human microsomal cytochrome P450 enzymes. Annu Rev Pharmacol Toxicol 29:241-264, 1989
21. Guengerich FP, Turvy CG: Comparison of levels of human microsomal cytochrome P450 enzymes and epoxide hydrolase in normal and disease status using immunochemical analysis of surgical samples. J Pharmacol Exp Ther 256: 1189-1194, 1991
22. Hunt CM, Westerkam WR, Stave GM: Effects of age and gender on the activity of human hepatic CYP3A. Biochem Pharmacol 44: 275-283, 1992
23. Watkins PB, Turgeon DK, Saenger P, et al: Comparison of urinary 6-beta-cortisol and the erythromycin breath test as measures of hepatic P450IIIA (CYP3A) activity. Clin Pharmacol Ther 52:265-273, 1992
24. Kinirons MT, O'Shea D, Downing TE, et al: Absence of correlations among three putative *in vivo* probes of human cytochrome P4503A activity in young healthy men. Clin Pharmacol Ther 54:621-629, 1993
25. Hunt CM, Watkins PB, Saenger P, et al: Heterogeneity of CYP3A isoforms metabolizing erythromycin and cortisol. Clin Pharmacol Ther 51:18-23, 1992
26. Thummel KE, Shen DD, Podoll TD, et al: Use of midazolam as a human cytochrome P450 3A probe: II. Characterization of inter- and intra-individual hepatic CYP3A variability after liver transplantation. J Pharmacol Exp Ther 271:557-566, 1994
27. Thummel KE, Shen DD, Podoll TD, et al: Use of midazolam as a human cytochrome P450 3A probe: I. In vitro-in vivo correlations in liver transplant patients. J Pharmacol Exp Ther 271: 549-556, 1994
28. Hirth J, Watkins PB, Strawderman M, et al: The effect of an individual's cytochrome CYP3A4 activity on docetaxel clearance. Clin Cancer Res 6:1255-1258, 2000
29. Goh BC, Lee SC, Wang LZ, et al: Explaining interindividual variability of docetaxel pharmacokinetics and pharmacodynamics in Asians through phenotyping and genotyping strategies. J Clin Oncol 20:3683-3690, 2002
30. Yamamoto N, Tamura T, Kamiya Y, et al: Correlation between docetaxel clearance and estimated cytochrome P450 activity by urinary metabolite of exogenous cortisol. J Clin Oncol 18:2301-2308, 2000
31. Yamaoka K, Nakagawa T, Uno T: Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. J Pharmacokinet Biopharm 6:165-175, 1978
32. Nakamura J, Yakata M: Determination of urinary cortisol and 6 beta-hydroxycortisol by high performance liquid chromatography. Clin Chim Acta 149:215-224, 1985
33. Lykkesfeldt J, Loft S, Poulsen HE: Simultaneous determination of urinary free cortisol and 6 beta-hydroxycortisol by high-performance liquid chromatography to measure human CYP3A activity. J Chromatogr B Biomed Appl 660:23-29, 1994
34. Vergniol JC, Bruno R, Montay G, et al: Determination of Taxotere in human plasma by a semi-automated high-performance liquid chromatographic method. J Chromatogr 582:273-278, 1992
35. Taguchi T, Furue H, Niitani H, et al: Phase I clinical trial of RP 56976 (docetaxel) a new anticancer drug. Gan To Kagaku Ryoho 21:1997-2005, 1994
36. Burris H, Irvin R, Kuhn J, et al: Phase I clinical trial of Taxotere administered as either a 2-hour or 6-hour intravenous infusion. J Clin Oncol 11:950-958, 1993
37. Extra JM, Rousseau F, Bruno R, et al: Phase I and pharmacokinetic study of Taxotere (RP 56976; NSC 628503) given as a short

intravenous infusion. Cancer Res 53:1037-1042, 1993

38. Pazdur R, Newman RA, Newman BM, et al: Phase I trial of Taxotere: Five-day schedule. J Natl Cancer Inst 84:1781-1788, 1992

39. Mathijssen RHJ, Verweij J, de Jonge MJ, et al: Impact of body-size measures on irinotecan clearance: Alternative dosing recommendations. J Clin Oncol 20:81-87, 2002

40. De Jongh FE, Verweij J, Loos WJ, et al: Body-surface area-based dosing does not increase accuracy of predicting cisplatin exposure. J Clin Oncol 19:3733-3739, 2001

41. Gurney HP, Ackland S, Gebski V, et al: Factors affecting epirubicin pharmacokinetics and toxicity: Evidence against using body-surface area for dose calculation. J Clin Oncol 16:2299-2304, 1998

42. Loos WJ, Gelderblom H, Sparreboom A, et al: Inter- and intrapatient variability in oral topotecan pharmacokinetics: Implications for body-surface area dosage regimens. Clin Cancer Res 6:2685-2689, 2000

43. Bruno R, Hille D, Riva A, et al: Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol 16:187-196, 1998

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Topoisomerase I Inhibitors in Small-Cell Lung Cancer

The Japanese Experience

ABSTRACT

Among patients with lung cancer, approximately 15% have small-cell lung cancer (SCLC). The clinical characteristics of SCLC tend to be more aggressive, but also more sensitive to chemotherapy and radiation therapy than those of non-SCLC. Irinotecan (Camptosar) is a derivative of camptothecin, an inhibitor of the nuclear enzyme topoisomerase I. Irinotecan has been shown to exhibit excellent antitumor activity against SCLC in monotherapy regimens and in combination with cisplatin. A phase III trial comparing irinotecan and cisplatin (IP) with etoposide and cisplatin (EP) in patients with previously untreated extensive-stage SCLC (ED-SCLC) was conducted. Patients in the IP arm responded significantly better than patients in the EP arm. In the IP arm, the response rate was 84%, and median overall survival was 12.8 months. A phase II trial of irinotecan, cisplatin, and etoposide (IPE) administered weekly (arm A) or every 4 weeks (arm B) for ED-SCLC (JCOG 9902-DI) was also performed. In arm B, the response rate was 77% and the median overall survival was 12.9 months. A randomized trial comparing IP with IPE administered every 3 weeks in patients with previously untreated ED-SCLC is presently being performed in Japan.

An estimated 75,000 new cases of lung cancer were diagnosed in Japan in 2002. Approximately 15% of these cases were diagnosed as small-cell lung cancer (SCLC), which is strongly associated with tobacco use, as is non–small-cell lung cancer (NSCLC). The clinical characteristics of SCLC tend to be more aggressive, but also more sensitive to chemotherapy and radiation therapy than those of NSCLC. Small-cell lung cancer is usually staged as either limited disease (LD) or extensive disease (ED).[1]

Platinum-based chemotherapy remains the mainstay of treatment regimens for ED-SCLC. In a meta-analysis of 19 randomized trials comparing a cisplatin-based regimen with a non–cisplatin-based regimen, patients randomized to a regimen containing cisplatin had a significantly higher probability of response and survival, with no significant increase in toxicity.[2] Berghmans et al presented a detailed analysis of the roles of etoposide and cisplatin in the treatment of SCLC.[3] Between 1980 and 1998, 36 eligible trials were performed. These trials concluded that the use of cisplatin and/or etoposide offered a significant survival advantage to patients with SCLC.

Irinotecan (Camptosar) has been semisynthesized as a water-soluble derivative of camptothecin, an inhibitor of nuclear enzyme topoisomerase I, in an attempt to reduce its toxicity and to improve its therapeutic efficacy.[4-8] In a phase II trial of irinotecan for SCLC, the response rate was 47%.[9,10] In preclinical studies, irinotecan and cisplatin exhibited synergistic activities. Their toxicity pro-

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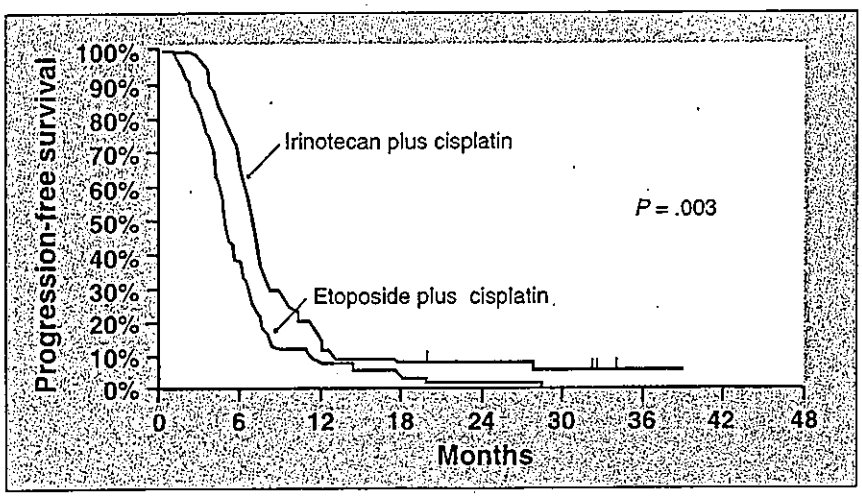

Figure 1: Progression-Free Survival—Progression-free survival of patients with extensive small-cell lung cancer who were assigned to treatment with irinotecan plus cisplatin or etoposide plus cisplatin (JCOG 9511).

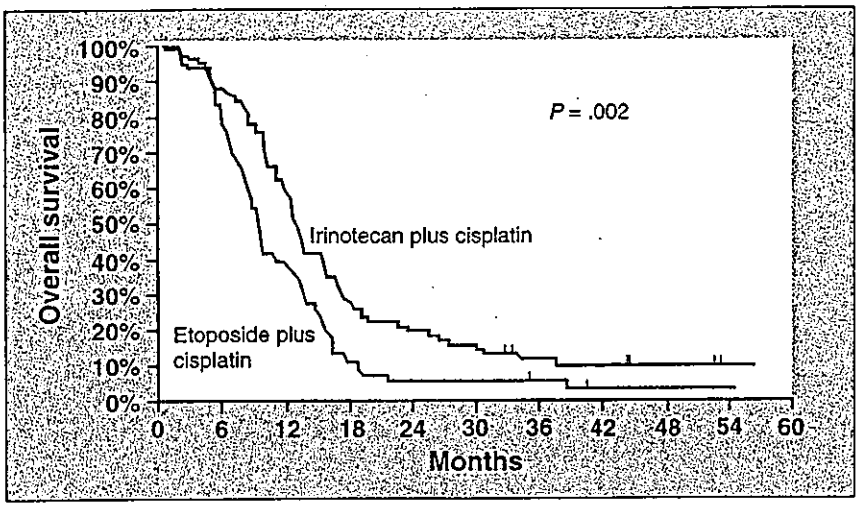

Figure 2: Overall Survival—Overall survival of patients with extensive small-cell lung cancer who were assigned to treatment with irinotecan plus cisplatin or etoposide plus cisplatin (JCOG 9511).

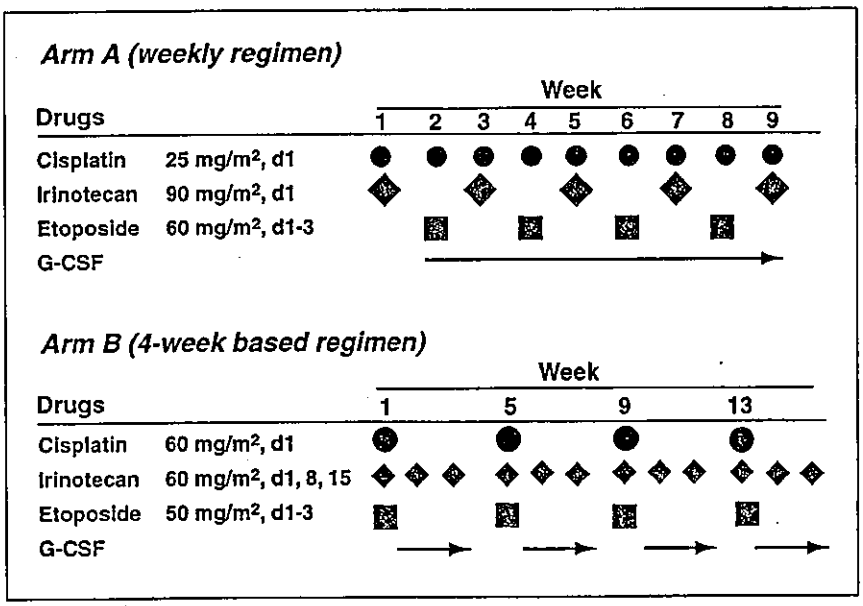

Figure 3: Study JCOG 9902-DI—Treatment schema of arm A (weekly regimen) and arm B (4-week regimen).

files also showed a minimal overlap.[11-16] In a phase II trial of irinotecan and cisplatin, the response rate was 86%.[17] In these trials, the principal toxicities were neutropenia and diarrhea.

Phase III Trial Comparing Irinotecan and Cisplatin With Cisplatin and Etoposide

Based on the results of the phase II trial, the Japan Clinical Oncology Group (JCOG) conducted a multiinstitutional randomized phase III trial (JCOG-9511) comparing irinotecan and cisplatin (IP) with cisplatin and etoposide (EP) in patients with previously untreated ED-SCLC.[18] The patient characteristics in this trial included an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and age ≤ 70 years. Patients with symptomatic central nervous system metastases requiring radiation or corticosteroid treatment were excluded from the trial. The experimental arm consisted of irinotecan at 60 mg/m² administered on days 1, 8, and 15 of each 4-week cycle, along with cisplatin at 60 mg/m² administered on day 1 for a total of four 4-week cycles (IP). This treatment regimen was compared with a regimen of etoposide at 100 mg/m² administered on the first 3 days of each 3-week cycle along with cisplatin at 80 mg/m² administered on day 1 for a total of four 3-week cycles (EP).

The principal end point was overall survival. The projected accrual for this trial was 230 patients (115 patients per arm). An interim analysis conducted after 77 patients had been accrued in each arm showed a significant survival advantage for the IP arm. Therefore, further enrollment in the trial was discontinued.

The response rate was significantly higher in the IP arm than in the EP arm (84% vs 68%; $P = .02$). Additionally, the IP arm showed a statistically significant improvement in both progression-free survival (6.9 vs 4.8 months; $P = .003$) (Figure 1) and median overall survival (12.8 vs 9.4 months; $P = .002$) (Figure 2).

The results of this trial were the most exciting to be seen in patients with previously untreated SCLC. The IP regimen is thus another platinum-based combination that should be considered for the treatment of ED-SCLC. Appropriately, the combination of cisplatin and irinotecan has become the new standard treatment for patients with ED-SCLC in Japan. However, several points must be examined before the IP regimen can be fully established as the new standard treatment for ED-SCLC. Three randomized controlled trials comparing the EP regimen with the IP regimen are presently under way in Europe and the United States.

Table 1

Patient Characteristics in JCOG 9902-DI

	Arm A (n = 30)		Arm B (n = 30)	
	Number of Patients	Percentage	Number of Patients	Percentage
Sex				
Female	3	10%	3	10%
Male	27	90%	27	90%
Median age (range)	64 yr	(47–70 yr)	63 yr	(46–68 yr)
Performance status				
0	2	7%	3	10%
1	25	83%	25	83%
2	3	10%	2	7%
Body weight loss				
< 5%	23	77%	21	70%
5%–10%	6	20%	8	27%
> 10%	1	3%	1	3%

Table 2

Number of Chemotherapy Cycles Delivered in JCOG 9902-DI

Arm A			Arm B		
Number of Cycles	Number of Patients	Percentage	Number of Cycles	Number of Patients	Percentage
9	22	73%	4	21	70%
8	4	13%	3	5	17%
5	1	3%	2	2	7%
4	1	3%	1	2	7%
2	1	3%			
1	1	3%			

Table 3

Total Administered Dosage and Dose Intensity Delivered in JCOG 9902-DI

	Arm A	Arm B
	Median (Range) Total Dosage	
Cisplatin	225 mg/m² (25–225 mg/m²)	240 mg/m² (60–240 mg/m²)
Irinotecan	450 mg/m² (90–450 mg/m²)	563 mg/m² (60–720 mg/m²)
Etoposide	720 mg/m² (0–720 mg/m²)	600 mg/m² (150–600 mg/m²)
	Median (Range) Dose Intensity	
Cisplatin	21 mg/m²/wk (13–25 mg/m² wk)	15 mg/m²/wk (12–15 mg/m²/wk)
Irinotecan	40 mg/m²/wk (21–90 mg/m²/wk)	35 mg/m²/wk (15–45 mg/m²/wk)
Etoposide	68 mg/m²/wk (0–80 mg/m²/wk)	37 mg/m²/wk (28–38 mg/m²/wk)

Table 4

Toxicity in JCOG 9902-DI

	Arm A (n = 30)		Arm B (n = 30)	
Toxicity (Grade 3/4)	Number of Patients	Percentage	Number of Patients	Percentage
Leukocytopenia	15	50%	16	53%
Neutropenia	17	57%	26	87%
Anemia	13	43%	14	47%
Thrombocytopenia	8	27%	3	10%
Infection	2	7%	4	13%
Diarrhea	2	7%	3	10%
Hyponatremia	4	13%	6	20%
CRN elevation	1	3%	1	3%
Treatment-related death	1	3%	0	0%

CRN = creatinine.

Phase II Trial of Cisplatin, Irinotecan, and Etoposide Administered Weekly or Every 4 Weeks

JCOG 9511 showed that the IP regimen was significantly better than the EP regimen. However, because etoposide was still considered to be a key drug in the treatment of SCLC, a combination of these three drugs—irinotecan, cisplatin, and etoposide (IPE)—seemed to be a promising strategy for the treatment of ED-SCLC. The recommended weekly doses (JCOG 9507) and the dosages for each 4-week cycle (JCOG 9512) for IPE were decided using dose-escalation trials. For these reasons, a phase II trial of irinotecan, cisplatin, and etoposide administered weekly or every 4 weeks for ED-SCLC (JCOG 9902-DI) was performed.[19]

The purpose of this trial was to evaluate the toxicity and antitumor effect of the combination of irinotecan, cisplatin, and etoposide administered according to two schedules, weekly (arm A) and every 4 weeks (arm B), for the treatment of previously untreated ED-SCLC, and to select the appropriate arm for use in phase III trials. Patients were enrolled in this trial if they met the following criteria: (1) a histologic or cytological diagnosis of SCLC; (2) no prior treatment; (3) measurable disease; (4) extensive disease, defined as distant metastasis or contralateral hilar lymph node metastasis; (5) performance status of 0 to 2 on the ECOG scale; (6) a life expectancy of 3 months or longer; (7) age between 20 and 70 years; (8) adequate organ function; and (9) written informed consent.

The treatment schedule is shown in Figure 3. In arm A, cisplatin at 25 mg/m² was administered intravenously (IV) over 60 minutes on day 1 and at 1-week intervals for 9 weeks; irinotecan at 90 mg/m² was administered IV over 90 minutes on day 1 on weeks 1, 3, 5, 7, and 9; and etoposide at 60 mg/m² was administered by IV over 60 minutes on days 1 to 3 of weeks 2, 4, 6, and 8. Granulocyte colony-stimulating factor (G-CSF) was administered prophylactically on the days when a cytotoxic drug was not given, unless the white blood cell (WBC) count exceeded 10.0×10^9/L.

In arm B, cisplatin at 60 mg/m² was administered by IV over 60 minutes on day 1; irinotecan at 60 mg/m² was administered by IV over 90 minutes on days 1, 8, and 15; and etoposide at 50 mg/m² was administered by IV over 60 minutes on days 1 to 3. G-CSF was injected subcutaneously from day 5 until the day when the WBC count exceeded 10.0×10^9/L. This treatment was repeated every 4 weeks for a total of four cycles.

Patient characteristics are listed in Table 1. Between August 1999 and October 2000, 30 patients were entered in each arm. The last follow-up

examination was performed in February 2002. All enrolled patients were included in the toxicity, tumor response, and patient survival analyses. No differences in any of the listed characteristics were observed between the two arms.

Treatment delivery is listed in Table 2. Of the 30 patients in each arm, 22 (73%) and 21 (70%) patients in arms A and B, respectively, received full cycles of chemotherapy (nine cycles in arm A and four cycles in arm B). Therapy was stopped because of toxicity in four (13%) patients in arm A and in six (20%) patients in arm B. Therapy was stopped because of tumor progression in three (10%) patients in each arm. The need for treatment delay in arm A and treatment skipping in arm B, however, was significant. Only eight (27%) patients in arm A completed the treatment without delay, and only seven (23%) patients in arm B received all the planned doses. A total of 105 chemotherapy cycles were administered to 30 patients in arm B, but eight (8%) doses of irinotecan on day 8, and 33 (31%) doses of irinotecan on day 15 were omitted because of toxicity, according to criteria in the protocol.

The median total dosages of cisplatin and etoposide administered per patient were maintained at the planned dosage levels in both arms (Table 3). The median total dosage of irinotecan as a percentage of the scheduled dosage (the relative total dosage) was 100% in arm A, but only 78% in arm B, reflecting the doses of irinotecan that were skipped on days 8 and 15.

Dose intensity was evaluated in 29 patients in arm A and 28 patients in arm B (Table 3). The median relative dosage intensity was well maintained at a level of 80% or higher, except that of irinotecan in arm B (77%). The median actual dosage intensity of etoposide was 70 mg/m²/wk in arm A and 37 mg/m²/wk in arm B.

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Table 5

Antitumor Responses in JCOG 9902-DI

	Arm A (n = 30)		Arm B (n = 30)	
Responses	Number of Patients	Percentage	Number of Patients	Percentage
Complete	2	7%	5	17%
Partial	23	77%	18	60%
No change	1	3%	0	0%
Progressive disease	3	10%	4	13%
No effect	1	3%	3	10%
Response rate	83% (95% CI = 65%–94%)		77% (95% CI = 58%–90%)	

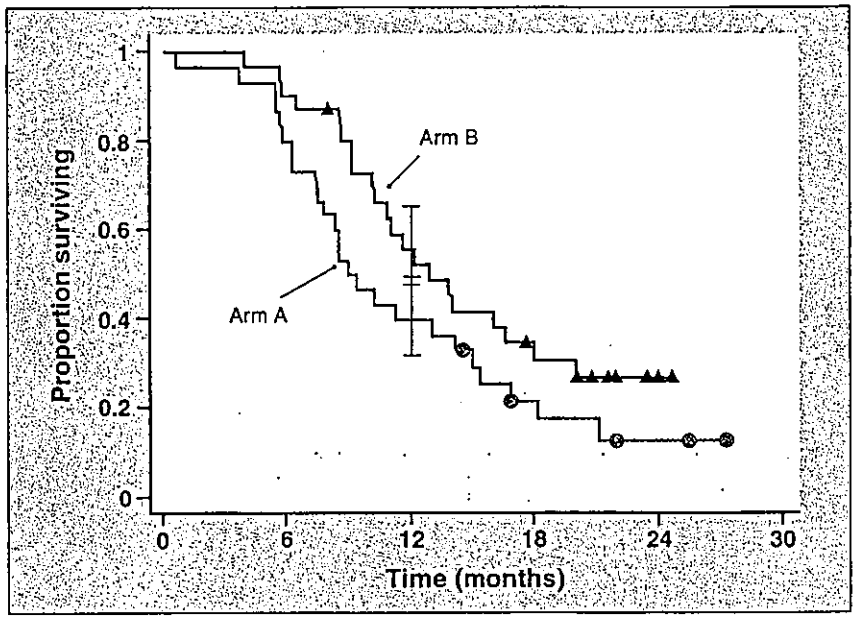

Figure 4: Study JCOG 9902-D1—Survival in treatment arms.

Toxicity was evaluated in all patients. The incidences of grade 3/4 neutropenia, anemia, thrombocytopenia, infection, and diarrhea in arm A were 57%, 43%, 27%, 7%, and 7%, respectively, and 87%, 47%, 10%, 13%, and 10%, respectively, in arm B. A treatment-related death occurred in one patient in arm A (Table 4).

Two complete responses (CRs) and 23 partial responses (PRs) were obtained in arm A, resulting in an overall clinical response rate of 83%, whereas five CRs and 18 PRs were obtained in arm B, resulting in an overall response rate of 77% (Table 5). The median time to survival and 1-year survival rate in arm A were 8.9

months and 40%, respectively, and 12.9 months and 57%, respectively, in arm B (Figure 4).

In this trial, the two IPE schedules were both effective against ED-SCLC and had an acceptable toxicity level. Arm B was adopted as the investigational arm in phase III trials.

Conclusion

The combination of cisplatin and irinotecan has become the new standard treatment for patients with ED-SCLC in Japan. However, SCLC is rarely cured, although the response rate has been improved and the survival time extended through the use of chemotherapy. Based on the results of JCOG 9511 and JCOG 9902-DI, a randomized trial comparing IP with IPE administered every 3 weeks in patients with previously untreated ED-SCLC is now being performed in Japan.

References

1. Kristjansen PE, Hansen HH: Management of small cell lung cancer: A Summary of the Third International Association for the Study of Lung Cancer Workshop on Small Cell Lung Cancer. *J Natl Cancer Inst* 82:263-266, 1990.

2. Pujol JL, Carestia L, Daures JP: Is there a case for cisplatin in the treatment of small-cell lung cancer?: A meta-analysis of randomized trials of a cisplatin-containing regimen vs a regimen without this alkylating agent. *Br J Cancer* 83:8-15, 2000.

3. Berghmans T, Paesmans M, Mascaux C, et al: A meta-analysis of the role of etoposide (VP-16) and cisplatin (CDDP) in small cell lung cancer (SCLC) with a methodology assessment (abstract). *Eur J Cancer* 35(suppl):S248, 1999.

4. Kunimoto T, Nitta K, Tanaka T, et al: Antitumor activity of 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy-camptothecin, a novel water-soluble derivative of camptothecin, against murine tumors. Cancer Res 47:5944-5947, 1987.

5. Matsuzaki T, Yokokura T, Mutai M, et al: Inhibition of spontaneous and experimental metastasis by a new derivative of camptothecin, CPT-11, in mice. *Cancer Chemother Pharmacol* 21:308-312, 1988.

6. Tsuruo T, Matsuzaki T, Matsushita M, et al: Antitumor effect of CPT-11, a new derivative of camptothecin, against pleiotropic drug-resistant tumors in vitro and in vivo. *Cancer Chemother Pharmacol* 21:71-74, 1988.

7. Taguchi T, Wakui A, Hasegawa K, et al: Phase I clinical study of CPT-11. *Gan To Kagaku Ryoho* 17:115-120, 1990. (in Japanese)

8. Ohno R, Okada K, Masaoka T, et al: An early phase II study of CPT-11: A new derivative of camptothecin, for the treatment of leukemia and lymphoma. *J Clin Oncol* 8:1907-1912, 1990.

9. Negoro S, Fukuoka M, Niitani H, et al: Phase II study of CPT-11, new camptothecin derivative, in small cell lung cancer (SCLC) (abstract). *Proc Am Soc Clin Oncol* 10:241, 1991.

10. Masuda N, Fukuoka M, Kusunoki Y, et al: CPT-11: A new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 10:1225-1229, 1992.

11. Kudoh S, Takada M, Masuda N, et al: Enhanced anti-tumor efficacy of a combination of CPT-11, a new derivative of camptothecin, and cisplatin against human lung tumor xenografts. *Jpn J Cancer Res* 84:203-207, 1993.

12. Masumoto N, Nakano S, Esaki T, et al: Inhibition of cis-diamminedichloroplatinum (II)-induced DNA interstrand cross-link removal by 7-ethyl-10-hydroxy-camptothecin in HST-1 human squamous-carcinoma cells. *Int J Cancer* 62:70-75, 1995.

13. Pei XH, Nakanishi Y, Takayama K, et al: Effect of CPT-11 in combination with other anticancer agents in lung cancer cells. *Anticancer Drugs* 8:231-237, 1997.

14. Masuda N, Fukuoka M, Kudoh S, et al: Phase I and pharmacologic study of irinotecan in combination with cisplatin for advanced lung cancer. *Br J Cancer* 68:777-782, 1993.

15. Masuda N, Fukuoka M, Kudoh S, et al: Phase I study of irinotecan and cisplatin with granulocyte colony-stimulating factor support for advanced non-small-cell lung cancer. *J Clin Oncol* 12:90-96, 1994.

16. Nakagawa K, Fukuoka M, Niitani H, et al: Phase II study of irinotecan (CPT-11) and cisplatin in patients with advanced non-small-cell lung cancer (NSCLC) (abstract). *Proc Am Soc Clin Oncol* 12:332, 1993.

17. Kudoh S, Fujiwara Y, Takada Y, et al: Phase II study of irinotecan combined with cisplatin in patients with previously untreated small-cell lung cancer. West Japan Lung Cancer Group. *J Clin Oncol* 16:1068-1074, 1998.

18. Noda K, Nishiwaki Y, Kawahara M, et al: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 346:85-91, 2002.

19. Sekine I, Nishiwaki Y, Noda K, et al: Randomized phase II study of cisplatin, irinotecan and etoposide combinations administered weekly or every 4 weeks for extensive small-cell lung cancer (JCOG9902-DI). *Ann Oncol* 14:709-714, 2003.

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Small-Cell Lung Cancer: Current Therapy and Novel Agents

ABSTRACT

Among patients with lung cancer, approximately 15% have small-cell lung cancer (SCLC). Although, without therapy, untreated SCLC is a rapidly proliferating tumor with a poor prognosis, response rates to chemotherapy and radiotherapy are high. SCLC is usually staged as either limited disease or extensive disease. Extensive disease is treated primarily with chemotherapy. A recent Japanese randomized trial compared IP (irinotecan [Camptosar]/cisplatin [Platinol]) with EP (etoposide/cisplatin). Patients in the IP arm had significantly better outcomes than patients in the EP arm. In the IP arm, the response rate was 84%, and the median overall survival period was 12.8 months. Limited disease is usually treated with concurrent chemotherapy and accelerated radiation therapy, and approximately 20% of patients are cured. Further investigations to improve local control and inhibit distant metastasis are clearly warranted. The dose-rate escalation in radiotherapy (administered concurrently with chemotherapy) is important in improving local control, and the introduction of molecular-targeting agents is necessary to inhibit distant metastasis.

An estimated 75,000 new cases of lung cancer were diagnosed in Japan in the year 2002, and approximately 15% of these cases were small-cell lung cancer (SCLC). Like non–small-cell lung cancer, SCLC is strongly associated with tobacco use. Left untreated, SCLC is a rapidly proliferating tumor with a poor prognosis, but response rates to chemotherapy and radiotherapy are high. SCLC is usually staged as either limited or extensive disease. The standard treatment for extensive disease is chemotherapy, and for limited disease is chemotherapy plus radiotherapy.

Nearly one-third of patients with SCLC present with limited disease, which is defined as disease confined to one hemithorax, without pericardial or pleural effusion, that can be encompassed by a single radiotherapy port.[1] Limited disease is a potentially more curable form of SCLC than extensive disease, and yet, before the use of chemotherapy, patients diagnosed with limited-stage SCLC survived an average of only 3 months.

History of Chemotherapy for SCLC

In the 1960s and 1970s, when cyclophosphamide (Cytoxan, Neosar) therapy was shown to be superior to best supportive care, the CAV regimen (cyclophosphamide/doxorubicin [Adriamycin]/vincristine) became standard treatment for SCLC. In the late 1970s, the effectiveness of EP chemotherapy (etoposide/cisplatin [Platinol]) was demonstrated in patients resistant to cyclophosphamide, and in the 1980s, EP became the standard rather than cyclophosphamide-based therapy. Given its mild side effects, the combination of radiotherapy and EP (without the need for drug dose reductions) subsequently became the standard approach.

In the late 1990s, the antitumor activities of new drugs such as paclitaxel, irinotecan (Camptosar), topotecan (Hycamtin), and amrubicin (investigational in the United States) were demonstrated in SCLC. Ongoing investigations are exploring the use of these agents, and the possibility that they might be more effective than EP.

Table 1

New Agents for the Treatment of Small-Cell Lung Cancer

Authors	Drug	Number of Patients	Prior Therapy	Response Rate
Negoro et al, 1991[5]	Irinotecan	27	Yes	33%
	Irinotecan	8	No	50%
Masuda et al, 1992[6]	Irinotecan	15	Yes	47%
Smyth et al, 1994[7]	Docetaxel	28	Yes	25%
Cormier et al, 1994[8]	Gemcitabine	26	No	27%
Ettinger et al, 1992[9]	Ifosfamide	43	No	49%
Ettinger et al, 1995[10]	Paclitaxel	32	No	34%
Kirschling et al, 1994[11]	Paclitaxel	37	No	41%
Ardizzoni et al, 1997[12]	Topotecan	47	Yes	6.4%
Schiller et al, 1996[13]	Topotecan	48	No	39%
Jassem et al, 1993[14]	Vinorelbine	25	Yes	16%
Furuse et al, 1996[15]	Vinorelbine	24	Yes	12.5%

In comparing state-of-the-art therapies for extensive and limited SCLC from 1981 and 2003, both median survival and 3-year survival rates have shown improvement. In this dataset, patient selection bias would presumably be a significant factor, but progress in therapy is critical to such improvement. The incorporation of new agents has been crucial in the establishment of more effective therapy.

Treatment of Extensive-Stage SCLC

Cisplatin and Etoposide

Platinum-based chemotherapy is the mainstay of treatment regimens for extensive disease. In a meta-analysis of 19 randomized trials comparing a cisplatin-based regimen with a non–cisplatin-based regimen, patients randomized to the regimen containing cisplatin had a significantly higher probability of response and survival, with no significant increase in toxicity.[2] Berghmans et al presented a detailed analysis of the roles of etoposide and cisplatin in the treatment of SCLC.[3] Thirty-six eligible trials were performed between 1980 and 1998; 1 trial compared cisplatin with no cisplatin, 17 compared etoposide with no etoposide, 9 compared cisplatin plus etoposide with no cisplatin plus etoposide, and 9 compared cisplatin plus etoposide with etoposide alone. These trials concluded that the use of cisplatin and/or etoposide offered a significant survival advantage to patients with SCLC.

In another meta-analysis, Chute et al evaluated all 21 cooperative group phase III trials performed in North America between 1972 and 1993.[4] Patients with extensive disease who were treated during a similar time interval and were listed in the Surveillance, Epidemiology, and End Results (SEER) database were also included in the analysis. The median survival time of patients in the control arms of the phase III trials initiated between 1972 and 1981 was 7.0 months; for those enrolled in control arms between 1982 and 1990, the median survival was 8.9 months ($P = .001$). Trends in the number of trials and the survival periods of patients over time were examined. A modest 2-month prolongation in median survival was demonstrated in patients with extensive disease. This improvement in survival was independently associated with both a cisplatin-based regimen and improvement in best supportive care measures.

Several other agents with significant activity in SCLC were studied in the 1990s (Table 1).[5-15]

Irinotecan

Irinotecan is a derivative of camptothecin, an inhibitor of nuclear enzyme topoisomerase I. Topoisomerase I creates single-strand breaks in DNA during DNA replication. Two trials have evaluated the use of irinotecan in patients with SCLC.[5,6] Negoro et al evaluated 35 patients, 27 of whom had received prior treatment.[5] Responses were seen in 9 of the 27 previously treated patients and 4 of the 8 previously untreated patients. The principal toxicities were neutropenia and diarrhea. Masuda et al studied 16 previously treated patients with SCLC.[6] Irinotecan (100 mg/m^2) was administered weekly, with dosages adjusted for toxicity. Responses were seen in 7 of the 15 evaluable patients, producing an overall response rate of 47%. The principal toxicities were diarrhea and neutropenia. Two patients suffered from grade 3 or 4 pulmonary toxicity, and one of these patients subsequently died.

Irinotecan's mechanism of action is complementary to that of cisplatin. Studies in preclinical models have shown that these two agents exhibit synergistic activities, and their toxicity profiles also show minimal overlap. For these reasons, irinotecan was an ideal drug for clinical trials with cisplatin as a first-line combined therapy.[16-18]

A phase II trial of cisplatin plus irinotecan as first-line combined therapy in patients with SCLC (including 35 patients with extensive disease) was conducted by the West Japan Thoracic Oncology Group. In this trial, both agents were administered at a dose of 60 mg/m^2; irinotecan was ad-

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ministered on days 1, 8, and 15 of each 28-day cycle, and cisplatin was administered on day 1.[19] For patients with extensive disease, the overall response rate was 86%, with 29% of patients achieving complete responses. The median survival was 13.0 months, with a 2-year survival rate of 17.5%.

Based on the results of this phase II trial, the Japan Clinical Oncology Group (JCOG) conducted a multi-institutional randomized phase III trial (JCOG-9511), comparing IP with EP in patients with previously untreated extensive disease.[20] The patient characteristics in this trial included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and an age of 70 years or less. Patients with symptomatic central nervous system metastases requiring radiation or corticosteroid treatment were excluded from the study. The experimental arm consisted of irinotecan (60 mg/m²) administered on days 1, 8, and 15 of each 4-week cycle, with cisplatin (60 mg/m²) administered on day 1 for a total of four 4-week cycles (IP). This treatment regimen was compared with a regimen of etoposide (100 mg/m²) administered on the first 3 days of each 3-week cycle, with cisplatin (80 mg/m²) administered on day 1 for a total of four 3-week cycles (EP). The principal end point was overall survival.

The projected accrual for this trial was 230 patients (115 patients per arm). An interim analysis conducted after 77 patients had been accrued in each arm showed a significant survival advantage for the IP arm. Therefore, further enrollment in the trial was discontinued. The response rate was significantly higher in the IP arm than in the EP arm (84% v 68%; $P = .02$). Additionally, the IP arm showed a statistically significant improvement in progression-free survival (6.9 vs 4.8 mo; $P = .003$) and median overall survival (12.8 vs 9.4 mo; $P = .002$; Figure 1).

The results of JCOG 9511 were the most provocative ever seen in patients with previously untreated SCLC. The IP regimen is thus another platinum-based combination that should be considered for the treatment of extensive disease. Appropriately, the combination of cisplatin and irinotecan has become the new standard treatment for patients with extensive disease in Japan.

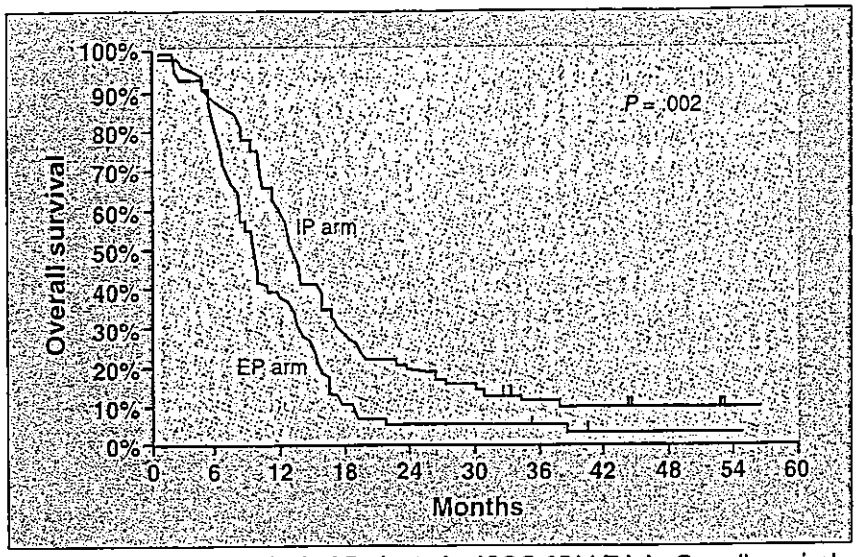

Figure 1: Overall Survival of Patients in JCOG 9511 Trial—Overall survival of patients with extensive small-cell lung cancer assigned to treatment with irinotecan plus cisplatin (IP) or etoposide plus cisplatin (EP). JCOG = Japan Clinical Oncology Group.

However, several points must be examined before the IP regimen is established as standard therapy worldwide. Clinical studies have been initiated to confirm these promising results by three groups: Pfizer, the Southwest Oncology Group (SWOG), and Aventis. The Pfizer group reported the interim results of this study as a North American study at ASCO 2003.[21] These investigators observed superior compliance and lower toxicity, as compared to the findings of JCOG 9511.

Amrubicin

Another excellent antitumor agent developed in Japan is amrubicin. In single-agent therapy, this drug produced a high response rate of 75.8% in extensive disease (median survival: 11.7 mo).[22] A phase II study of amrubicin plus cisplatin demonstrated a response rate of 86.8%.[23]

Etoposide/Cisplatin–Based Combinations

Another approach to improving efficacy is the addition of new agents to EP therapy. Phase II/III studies of a regimen known as PET (cisplatin, etoposide, paclitaxel [Taxol]) have been performed in the United States. In a phase II study with 80 patients, the response rate was 57%, median survival was 11 months, and treatment-related death was 14%.[24] The results of a controlled study comparing EP with PET in 572 patients showed a slightly superior complete response rate in the PET arm, but there was no difference in median survival or the 1-year survival rate between the two therapy arms, Moreover, grade 5 toxicity was higher in the PET arm.[25].

A phase II trial of irinotecan/cisplatin/etoposide (IPE) administered weekly (arm A) or every 4 weeks (arm B) for extensive disease (JCOG 9902-DI) was also performed. In arm B, the response rate was 77%, and median survival was 12.9 months.[26] A randomized trial comparing IP with IPE administered every 3 weeks in patients with previously untreated extensive disease is currently being conducted in Japan.

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Molecular-Targeted Therapy

Although there are many controlled studies comparing dose-intensive weekly chemotherapy with non–cross-resistant alternative chemotherapy, solid data have yet to be obtained. Molecular-targeted therapy has also been investigated in SCLC, but at this time, no agents in this class have proven effective against the disease.

There are no reported cases of a response to either a farnesyl transferase inhibitor among previously treated SCLC patients, or to imatinib mesylate (Gleevec) among untreated SCLC patients. A controlled study comparing marimastat (investigational in the United States) after four cycles of EP with a placebo showed no difference in survival and significantly greater toxicity in the marimastat arm.[27] At ASCO 2003, the optimal dose of oblimersen sodium (Genasense), an investigational Bcl-2 inhibitor, was evaluated in combination therapy with etoposide and carboplatin (Paraplatin). A randomized trial to assess the combination of oblimersen, etoposide, and carboplatin in SCLC will be conducted by the Cancer and Leukemia Group B (CALGB).[28] Furthermore, neither vascular endothelial growth factor (VEGF) nor cyclooxygenase (COX)-2 expression is reportedly a significant prognostic factor in SCLC.[29]

Reference Guide

Therapeutic Agents Mentioned In This Article

- Amrubicin
- Carboplatin (Paraplatin)
- Cisplatin
- Cyclophosphamide (Cytoxan, Neosar)
- Doxorubicin
- Etoposide
- Imatinib mesylate (Gleevec)
- Irinotecan (Camptosar)
- Marimastat
- Oblimersen sodium (Genasense)
- Paclitaxel
- Topotecan (Hycamtin)
- Vincristine

Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.

Recurrent Disease

Most SCLC patients are destined to relapse, and the prognosis of these relapsed patients is poor. No standard therapy for patients with recurrent SCLC after a complete response has been established. Patients who relapse less than 3 months after first-line therapy are commonly called refractory, and those who relapse at least 3 months after therapy are called sensitive. Sensitive cases may be re-treated with the same induction regimen used initially. Refractory patients who are in satisfactory clinical condition should be offered a second-line regimen. Such patients are usually registered in a phase I or phase II study of new antitumor agents, such as topotecan, irinotecan, or paclitaxel.[30-32]

Elderly Patients

The proportion of elderly patients among all lung cancer cases is rapidly increasing with the aging of society. In many of these cases, general chemotherapy is not feasible due to unsatisfactory performance status, and treatment of such patients should be a focus of future research. Although there is no difference in survival between elderly and other populations, the death rate due to toxicity is high in the elderly population. A trial of oral etoposide among patients who did not respond to CAV was reported (and its use in elderly patients was anticipated), but a later controlled study revealed higher toxicity and less efficacy with the oral agent, compared to standard chemotherapy.[33,34] Recently, oral etoposide has not been used as a single agent.

Treatment of Limited-Stage SCLC

SCLC has long been recognized to be clinically responsive to radiation therapy, and in vitro irradiation of SCLC cell lines has shown that they often have a greater intrinsic radiosensitivity than adenocarcinomas or squamous cell lung cancer cell lines. Consequently, many early trials combining radiation therapy with chemotherapy in patients with SCLC used low total radiation dosages.

A number of trials conducted in the 1970s and 1980s compared chemotherapy alone with chemotherapy and thoracic radiation therapy in patients with limited disease. These trials varied with regard to the radiation dosage, timing, and choice of chemotherapeutic agents used. Warde and Payne analyzed these trials and found that the addition of thoracic radiation therapy improved local control and survival rates.[35] Pignon et al obtained individual patient data from these trials and updated the analyses after their original publication.[36] They found that the addition of thoracic radiation therapy increased the 3-year survival rate from 8.9% to 14.3%—an absolute improvement of 5% and a relative improvement of nearly 50%.

In the 1990s, several trials examined whether radiation therapy and chemotherapy should be administered concurrently or sequentially and whether radiation therapy should be administered early or late in the overall course of treatment. Murray and Coldman performed a meta-analysis of trials that combined chemotherapy and thoracic radiation therapy, using 3-year progression-free survival as a surrogate end point for long-term survival.[37] The best results were seen when thoracic radiation therapy was administered 3 to 5 weeks after the start of chemotherapy. When radiation therapy was further delayed, the survival benefit decreased and approached that seen with chemotherapy alone.

The rapid growth of many SCLC cell lines encouraged the exploration of accelerated radiation treatment schedules, with two fractions administered per day and a modest reduction in fraction size from the usual 1.8–2.0 Gy to 1.5 Gy. Two prospective trials compared this approach with conventional daily fractionation. Tur-

risi et al compared 45-Gy doses administered in 25 fractions for more than 5 weeks with 45-Gy doses administered in 30 fractions for more than 3 weeks. The chemotherapy regimen in this study consisted of four cycles of cisplatin plus etoposide. The accelerated regimen resulted in an improved local control rate (intrathoracic failure in the accelerated therapy arm was 36%; in the standard therapy arm, 52%) and 5-year survival rate (twice-daily regimen: 26%; standard regimen: 16%). Although an increased incidence of grade 3 esophagitis (26% vs 11%, respectively) was observed, no other significant differences in toxicity were seen.[38]

Conclusions

The incidence of SCLC has been decreasing. In 1998, SCLC reportedly accounted for only 13.8% of all lung cancers. A two-tiered staging system is generally utilized for diagnosis. Platinum-based chemotherapy is the standard treatment for extensive disease. The cisplatin/irinotecan combination has become the new standard treatment for patients with extensive disease in Japan. Limited disease is treated with concurrent chemotherapy and accelerated radiation therapy, enabling approximately 20% of all patients to be cured.

Future investigation of strategies to improve local control and inhibit distant metastasis is warranted. To improve local control, researchers need to explore dose-rate escalation of radiotherapy administered concurrently with chemotherapy, and for inhibiting distant metastasis, molecular-targeting agents are an important approach.

This article is reviewed on pages 52, 55, and 57.

References

1. Kristjansen PE, Hansen HH: Management of small cell lung cancer: A Summary of the Third International Association for the Study of Lung Cancer Workshop on Small Cell Lung Cancer. *J Natl Cancer Inst* 82:263-266, 1990.
2. Pujol JL, Carestia L, Daures JP: Is there a case for cisplatin in the treatment of small-cell lung cancer? A meta-analysis of randomized trials of a cisplatin-containing regimen vs a regimen without this alkylating agent. *Br J Cancer* 83:8-15, 2000.
3. Berghmans T, Paesmans M, Mascaux C, et al: A meta-analysis of the role of etoposide (ETP) and cisplatin (CDDP) in small cell lung cancer (SCLC) with a methodology assessment (abstract). *Eur J Cancer* 35(suppl):s248, 1999.
4. Chute, JP, Chen, T, Feigal E, et al: Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: Perceptible progress. *J Clin Oncol* 17:1794-1801, 1999.
5. Negoro S, Fukuoka M, Niitani H, et al: Phase II study of CPT-11, new camptothecin derivative, in small cell lung cancer (SCLC) (abstract). *Proc Am Soc Clin Oncol* 10:241a, 1991.
6. Masuda N, Fukuoka M, Kusunoki Y, et al: CPT-11: A new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 10:1225-1229, 1992.
7. Smyth JF, Smith IE, Sessa C, et al: Activity of docetaxel (Taxotere) in small cell lung cancer. *Eur J Cancer* 30A:1058-1060, 1994.
8. Cormier Y, Eisenhauer E, Muldal A, et al: Gemcitabine is an active new agent in previously untreated extensive small cell lung cancer (SCLC). National Cancer Institute of Canada Clinical Trials Group. *Ann Oncol* 75:283-285, 1994.
9. Ettinger D, Finkelstein D, Ritch P, et al: Randomized trial of single agents vs combination chemotherapy in extensive stage small cell lung cancer (SCLC) (abstract 988). *Proc Am Soc Clin Oncol* 11:295a, 1992.
10. Ettinger D, Finkelstein DM, Sarma RP, et al: Phase II study of paclitaxel in patients with extensive-disease small cell lung cancer: An Eastern Cooperative Oncology Group study. *J Clin Oncol* 13:1430-1435, 1995.
11. Kirschling RJ, Jung SH, Jett JR, et al: A phase II trial of Taxol and GCSF in previously untreated patients with extensive stage small cell lung cancer (SCLC) (abstract 1076). *Proc Am Soc Clin Oncol* 13:326a, 1994.
12. Ardizzoni A, Hansen H, Dombernowsky P, et al: Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: A phase II study in patients with refractory and sensitive disease. The European Organization for Research and Treatment of Cancer Early Clinical Studies Group and New Drug Development Office, and the Lung Cancer Cooperative Group. *J Clin Oncol* 15:2090-2096, 1997.
13. Schüller JH, Kim K, Hutson P, et al: Phase II study of topotecan in patients with extensive-stage small-cell carcinoma of the lung: An Eastern Cooperative Oncology Group Trial. *J Clin Oncol* 14:2345-2352, 1996.
14. Jassem J, Karnicka-Mlodkowska H, Van Pottelsberghe CH, et al: Phase II study of vinorelbine (navelbine) in previously treated small cell lung cancer patients. *Eur J Cancer* 29A:1720-1722, 1993.
15. Furuse K, Kubota K, Kawahara M, et al: Phase II study of vinorelbine in heavily previously treated small cell lung cancer. *Oncology* 53:169-172, 1996.
16. Kudoh S, Takada M, Masuda N, et al: Enhanced anti-tumor efficacy of a combination of CPT-11, a new derivative of camptothecin, and cisplatin against human lung tumor xenografts. *Jpn J Cancer Res* 84:203-207, 1993.
17. Masumoto N, Nakano S, Esaki T, et al: Inhibition of cis-diamminedichloroplatinum (II)-induced DNA interstrand cross-link removal by 7-ethyl-10-hydroxy-camptothecin in HST-1 human squamous-carcinoma cells. *Int J Cancer* 62:70-75, 1995.
18. Pei XH, Nakanishi Y, Takayama K, et al: Effect of CPT-11 in combination with other anticancer agents in lung cancer cells. *Anticancer Drugs* 8:231-237, 1997.
19. Kudoh S, Fujiwara Y, Takada Y, et al: Phase II study of irinotecan combined with cisplatin in patients with previously untreated small-cell lung cancer. *J Clin Oncol* 16:1068-1074, 1998.
20. Noda K, Nishiwaki Y, Kawahara M, et al: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 346:85-91, 2002.
21. Sandler A, Langer C, Bunn PA, et al: Interim safety analysis of irinotecan and cisplatin combination chemotherapy for previously untreated extensive small cell lung cancer (abstract 2537). *Proc Am Soc Clin Oncol* 22:631, 2003.
22. Yana T, Negoro S, Takada Y, et al: Phase II study of amrubicin (SM-5887), a 9-aminoanthracycline, in previously untreated patients with extensive stage small-cell lung cancer (ES-SCLC): A west Japan lung cancer group trial (abstract). *Proc Am Soc Clin Oncol* 17:450a, 1998.
23. Negoro S, Ohe Y, Matsui K, et al: Phase I-II study of amrubicin and cisplatin in previously untreated patients with extensive stage small cell lung cancer (ED-SCLC) (abstract 2608). *Proc Am Soc Clin Oncol* 22:648, 2003.
24. Kelly K, Lovato L, Bunn PA Jr, et al: Cisplatin, etoposide, and paclitaxel with granulocyte colony-stimulating factor in untreated patients with extensive-stage small cell lung cancer: A phase II trial of the Southwest Oncology Group. *Clin Cancer Res* 7:2325-2329, 2001.
25. Niell HB, Herndon JE, Miller AA, et al: Randomized phase III intergroup trial (CALGB 9732) of etoposide (ETP) and cisplatin (DDP) with or without paclitaxel (TAX) and G-CSF in patients with extensive stage small cell lung cancer (ED-SCLC) (abstract 1169). *Proc Am Soc Clin Oncol* 21:293a, 2002.
26. Sekine I, Nishiwaki Y, Noda K, et al: Randomized phase II study of cisplatin, irinotecan and etoposide combinations administered weekly or every 4 weeks for extensive small-cell lung cancer (JCOG9902-DI). *Ann Oncol* 14:709-714, 2003.
27. Shepherd FA, Giaccone G, Seymour L, et al: Prospective, randomized, double-blind, placebo-controlled trial of marimastat after response to first-line chemotherapy in patients with small-cell lung cancer: A trial of the National Cancer Institute of Canada-Clinical Trials Group and the European Organization for Research and Treatment of Cancer. *J Clin Oncol* 15:4434-4439, 2002.