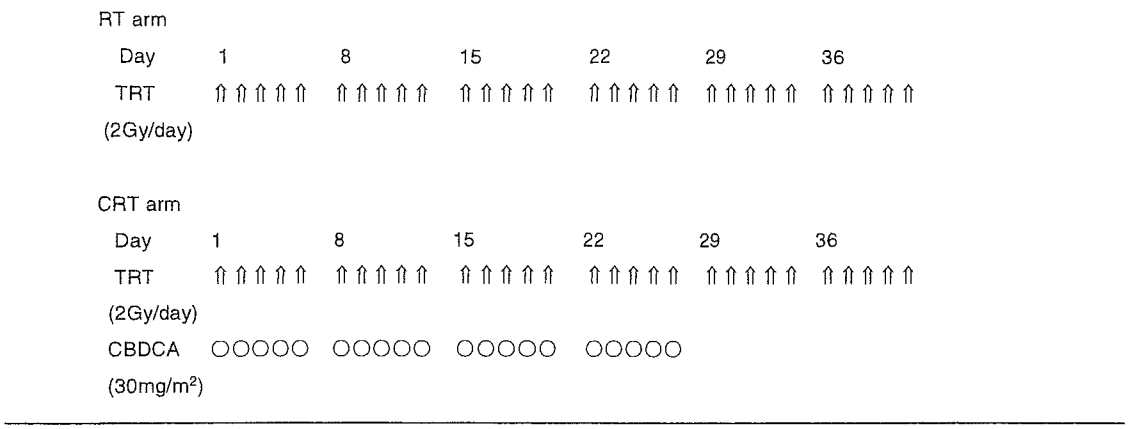


RT, radiotherapy; CRT, chemotherapy; TRT, thoracic radiotherapy; CBDCA, carboplatin.

Figure 1. Treatment schema.

Study Design and Statistical Analysis

This trial was a multi-center randomized phase III study. The study protocol was approved by the JCOG Clinical Trials Review Committee and the institutional review board of each participating institution before the initiation of the study.

The primary end-point was overall survival, which was defined as the interval from randomization to death from any cause. Secondary end-points were response rate, which was the proportion of the patients evaluated as having a complete reponse (CR) or partial response (PR) in best overall response out of all eligible patients; progression-free survival (PFS) defined as the interval from randomization to the diagnosis of progression or death from any cause; sites of progression; and toxicity. The estimate of survival time was performed by the Kaplan–Meier method (31). The trial was designed to have an 80% power to detect 5 months difference in MST (10 months in the RT arm and 15 months in the CRT arm) with a one-sided alpha of 0.05 by log rank test (32). The planned sample size was 190 patients by Shoenfeld and Richter's methods (33) with 1.5 years follow-up after 3 years accrual.

In-house interim monitoring is performed by the JCOG Data Center to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. The monitoring reports are submitted and reviewed by the JCOG Data and Safety Monitoring Committee (DSMC) twice yearly.

An expedited report was required by the JCOG DSMC to allow rapid identification of any life-threatening adverse events or unexpected toxicities according to the JCOG toxicity reporting system based on the ICH-E2A guidelines.

RESULTS

From November 1999 to February 2001, 46 patients were enrolled in this study: 23 in the RT arm and 23 in the CRT arm. Four treatment-related deaths (TRDs) had been reported, however, before the forty-sixth patient were assigned. Therefore, we suspended the registration and checked the details of all randomized patients to assess the safety of treatment regimens. As a result, it was revealed that three of these deaths were due to pneumonitis. The JCOG DSMC advised consultation with the JCOG Radiotherapy Committee (RC) about the radiotherapy compliance in all patients. The JCOG RC collected each patient's irradiation planning data retrospectively and found poor protocol compliance which was related to TRD. Consequently, we decided to terminate this trial in August 2001 following the recommendation of the JCOG DSMC.

PATIENTS CHARACTERISITICS

Patient characteristics are listed in Table 1. No specific characteristics of patients were found in the elderly patients with locally advanced NSCLC compared with younger patiests and the two treatment arms were well balanced with respect to age and stage.

Toxicity of Treatment

Both hematological and non-hematological toxicities during the treatment and follow-up period were assessed. Table 2 summarizes the hematological toxicity. Patients receiving CBDCA suffered from leukocytopenia, neutropenia and thrombocytopenia more than patients receiving RT alone. There was no grade 4 hematological toxicity in the RT arm. Two (8.7%) and four (17.4%) patients in the CRT arm experienced grade 4 leukocytopenia and neutropenia, respectively.

Non-hematological toxicity observed in this study is listed in Table 3. None of the patients developed grade 3 esophagitis in either treatment arm. In the RT arm, other grade 3/4 toxicities were edema, fatigue, dyspnea and pneumonitis in one patient each. In the CRT arm, other grade 3/4 toxicities were neutropenic fever, dyspnea and pneumonitis. Grade 3/4 (RTOG/EORTC Radiation Toxicity Score) of late lung toxicity was observed in two patients in the RT arm and four patients in the CRT arm. Four TRDs were observed in this study. Three of

Table 1. Patient characteristics

Characteristics	RT arm	CRT arm
No. of eligible patients	23	23
Age (years)		
Median	77	77
Range	72–84	71–83
Male/female	19/4	16/7
Type of tumor		
Adenocarcinoma	6	11
Squamous cell	16	11
Large cell	1	1
PS (ECOG)		
0	3	9
1	19	13
2	1	1
Stage of disease		
IIIA	11	12
IIIB	12	11
Weight loss		
<10%	21	23
≥10%	2	0

RT, radiotherapy; CRT, chemoradiotherapy; PS, performance status.

Table 2. Hematological toxicity

	RT arm (n = 23)					CRT arm (n = 23)				
Grade	1	2	3	4	%grade 4	1	2	3	4	%grade 4
Leukocytes	10	2	2	0	0	3	7	11	2	8.7
Neutrophils	4	3	0	0	0	2	8	6	4	17.4
Hemoglobin	5	3	0	0	0	5	8	3	0	0
Platelets	2	0	2	0	0	4	5	8	0	0

RT, radiotherapy; CRT, chemoradiotherapy.

these patients were thought to have died as a result of pneumonitis. The details of these cases are follows. Case 1: a 78-year-old man had stage IIIA (T3N2) squamous cell carcinoma. He was treated with RT alone and died of pneumonitis at 28 days after therapy. Case 2: a 79-year-old man had stage IIIB (T4N2) adenocarcinoma. He was treated with CBDCA + RT and died of bacterial pneumonia at 37 days after therapy and had been taking steroid hormone due to radiation pneumonitis. Case 3: a 73-year-old man had stage IIIA (T3N2) squamous cell carcinoma. He was treated with CBDCA + RT and died of pneumonitis at 80 days after therapy. Case 4: a 80-year-old man had stage IIIB (T4N2) squamous cell carcinoma. He was treated with CBDCA + RT and died of pneumonitis at 54 days after therapy. Thus, three out of four TRDs were in the CRT arm and one was in the RT arm.

Table 3. Non-hematological toxicity

	RT arm (n = 23)					CRT arm (n = 23)				
Grade	1	2	3	4	% grade 4	1	2	3	4	% grade 4
Edema	0	0	0	1	4.5	0	0	0	0	0
Fatigue	1	0	0	1	4.5	7	1	0	0	0
Fever	3	0	0	0	0	1	1	0	0	0
Esophagitis	13	2	0	0	0	10	2	0	0	0
Nausea	0	0	0	–	–	2	2	0	–	–
Vomiting	0	0	0	0	0	1	0	0	0	0
Febrile neutropenia	–	–	0	0	0	–	–	1	0	0
Cough	3	1	0	–	–	6	0	0	–	–
Dyspnea	–	0	0	1	4.5	–	2	1	0	0
Pneumonitis	1	0	0	–	4.5	1	0	1	0	0
Creatinine	1	0	0	0	0	0	0	0	0	0
Hyponatremia	7	–	0	0	0	5	–	1	0	0
Heart	0	0	0	0	0	0	1	0	0	0
Lung	8	4	2	0	0	9	6	1	3	13.0

RT, radiotherapy; CRT, chemoradiotherapy.

Protocol Compliance

In the RT arm, 22 (95.6%) patients received full treatment doses. In the CRT arm, 20 (87.0%) patients completed the treatment. As to the administration of CBDCA, there were few protocol deviations.

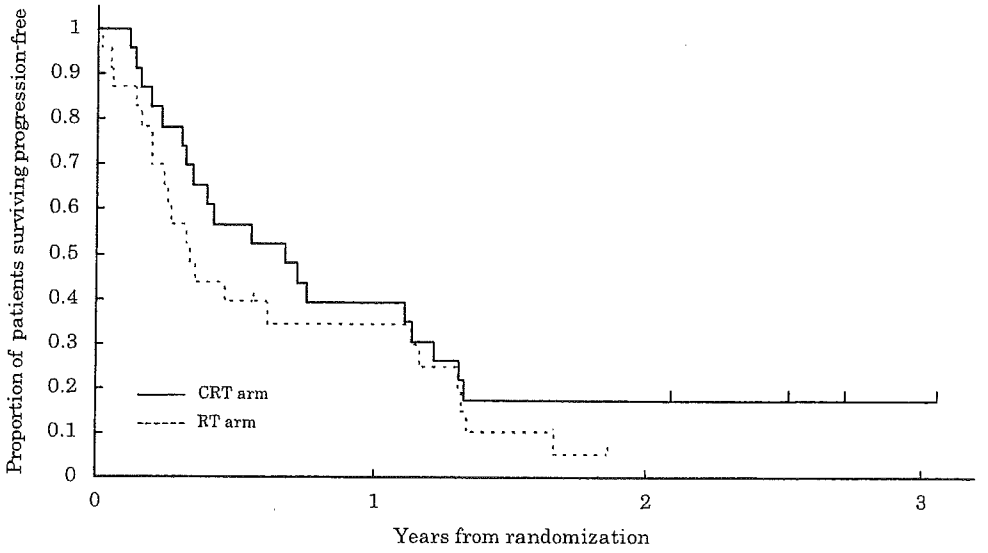
Three of the patients discontinued the protocol treatment: one was due to grade 2 eruption, one was due to cerebral infarction and one was due to insufficient recovery from leukopenia. One patient in the RT arm did not start the treatment due to local progression (Table 4).

Quality Assurance of Radiotherapy

We evaluated the quality of radiotherapy retrospectively based on the collected radiation therapy planning data. The data of 45 patients were reviewed and evaluated for the analysis. Details of this analysis have been reported by Ishikura et al. (34); three cases were revealed to be protocol violation due to normal lung volume constraint defined in the protocol. Unacceptable protocol deviations were identified as follows; 17, 15 and 31 cases on field border placement for the primary tumor, the metastatic lymph nodes and the elective nodal irradiation, respectively. Overall, 27 of 45 cases (60%) had at least one unacceptable deviation. Most cases judged to have protocol violation were primarily due to a smaller radiation field. Only 18 cases (40%) were judged to be protocol compliant.

Response and Survival

The tumor response in each arm is listed in Table 5. No patients achieved a CR in either arm. Of the 23 patients in the RT arm, 12 [52.2%, 95% confidence interval (CI) = 30.6–73.2%] achieved PR and six (26.1%) had stable disease. Of the



RT, radiotherapy; CRT, chemoradiotherapy.

Figure 2. Progression-free survival for patients treated with radiation alone or radiation with concurrent daily CBDCA.

Table 4. Protocol compliance

Pattern	RT arm (n = 23)	CRT arm (n = 23)
Complete protocol treatment	22	20
Progression/relapse*	1	0
Adverse events		
Cerebral infarction	0	1
Eruption	0	1
Leukopenia	0	1
Patient refusal	0	0
Death on protocol	0	0
Other	0	0

*Before starting the radiotherapy.
RT, radiotherapy; CRT, chemoradiotherapy.

Table 5. Response to treatment

Response	RT arm (n = 23)	CRT arm (n = 23)
Complete response	0 (0)	0 (0)
Partial response	12 (52.2)	11 (47.8)
Stable disease	6 (26.1)	7 (30.4)
Progression	4 (17.4)	4 (17.4)
Not evaluable	1 (4.4)	1 (4.4)
Objective response	52.2%	47.8%

RT, radiotherapy; CRT, chemoradiotherapy.

23 patients in the CRT arm, 11 (47.8%, 95% CI = 26.8–69.4%) achieved PR and seven (30.4%) had stable disease.

Seventeen (73.9%) patients in the RT arm and 15 (65.2%) patients in the CRT arm had died at the time of analysis. The median progression-free survival time was 122 days (95% CI = 88–413 days) on the RT arm versus 248 days (95% CI = 127–416 days) on the CRT arm (Fig. 2.). The MST was 428 days (95% CI = 212–680 days) on the RT arm versus 554 days (95% CI = 331 to not estimable) on the CRT arm (Fig. 3.). The 1-year survival rate was 60.9% (95% CI = 40.9–80.8%) on the RT arm versus 65.2% (95% CI = 45.8–84.7%) on the CRT arm.

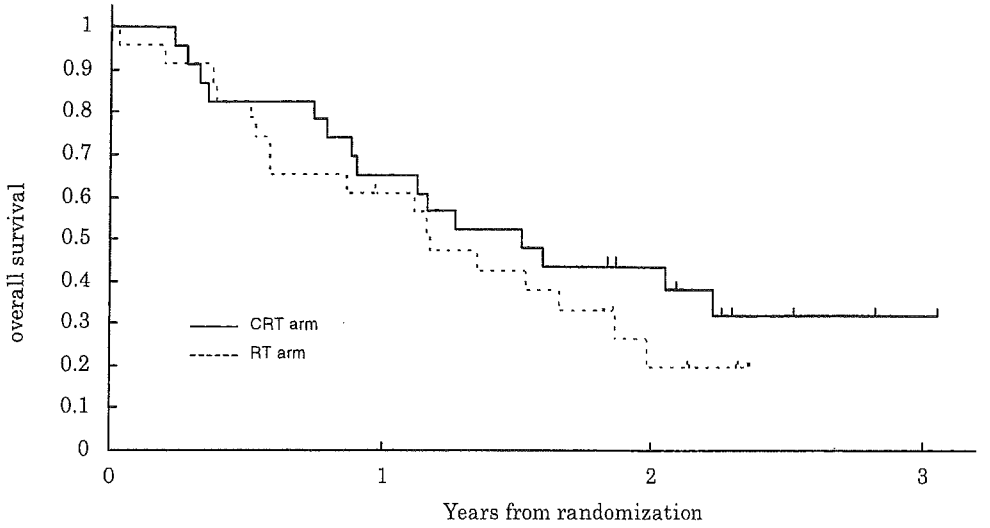
Pattern of Progression/Relapse

The first site of disease progression or relapse is listed in Table 6. Sixteen patients in the RT arm and 13 patients in the CRT arm had relapsed or had disease progression at the time of analysis. Eight patients (out of 16, 50.0%) in the RT arm and seven patients (out of 13, 53.8%) in the CRT arm had relapse or disease progression within the radiation field whether relapse outside the radiation field occurred or not.

DISCUSSION

We conducted this randomized controlled trial to determine whether chemoradiotherapy was superior to radiotherapy alone with respect to overall survival of elderly patients with locally advanced NSCLC. The study was terminated early when 24% of the planned sample size was accrued because of a high proportion of TRDs due to radiation pneumonitis and protocol violation.

Pulmonary toxicities including radiation pneumonitis and fibrosis caused by radiation therapy are, in general, common but not severe. In this study, however, the risk of TRD was 8.7% (four out of 46) and was much higher than in other trials. For instance, Ohe et al. (35) retrospectively analyzed the incidence of TRDs in the treatment of thoracic radiotherapy and/or chemotherapy for patients with locally advanced NSCLC, and reported that seven of 448 patients (1.6%)



RT, radiotherapy; CRT, chemoradiotherapy.

Figure 3. Overall survival for patients treated with radiation alone or radiation with concurrent daily CBDCA.

Table 6. First site of disease progression

	RT arm (n = 23)	CRT arm (n = 23)
Local	8	5
Distant	8	6
Local + distant	0	2

RT, radiotherapy; CRT, chemoradiotherapy.

died of radiation-induced pneumonitis. The high proportion of pulmonary toxicities in our trial may be due partly to the high age of the patients. Schild et al. (15) reported that they found 6% of elderly (older than 75 years) with NSCLC had grade 4 pneumonitis whereas this was the case in only 1% of younger patients ($P = 0.02$). It was controversial that the four TRDs out of 46 was sufficient reason to terminate the on-going trial; however, we thought it was serious that half of the TRDs (two out of four) were judged to be associated with protocol violation concerning the radiation field, which was to be less than half of one lung. Because the JCOG had not yet established the quality control/assurance system for radiotherapy before this trial, we concluded that we would not be able to control the risk of radiation pnuemonitis due to protocol deviation if we continued this study. What was an issue in this study was not only the high TRD rate, but also the poor protocol compliance of RT. The reasons for the poor protocol compliance are limited participation of radiation oncologists during protocol development, limited educational resources for attending radiation oncologists and no quality control program. Although the retrospective systematic review of radiation planning and protocol compliance of radiotherapy was the first experience in the JCOG, both the Lung Cancer Study Group and the entire JCOG had become aware of the importance of a quality control system for radiotherapy. The JCOG Executive Committee decided to establish the Radiation Therapy Quality Assurance Center (RTQAC) within the JCOG Data Center under the supervision of the JCOG Radiotherapy Committee. The RTQAC started the prospective quality control and quality assurance (QC/QA) program in September 2002 with a new activated phase III study for limited disease of small cell lung cancer, JCOG0202. Up to 2004, the QC/QA program has been expanded to the other group studies, such as esophageal cancer study, breast cancer study, prostate cancer study and brain tumor study. In addition, the JCOG Executive Committee mandates the QC/QA program by the RTQAC for all JCOG trials when protocol treatment includes radiation therapy.

The clinical question raised in this trial has not been answered. The data from the 46 patients enrolled were not considered to be conclusive because of the small sample size. No remarkable difference was found between the arms in terms of safety and efficacy such as tumor response, PFS and overall survival. We considered that it still remained an important clinical question to be investigated whether the daily low-dose CBDCA plus radiotherapy was effective or not. Therefore, we re-planned and started a new phase III trial (JCOG0301), in which the prospective QC/QA program by the RTQAC is added to the identical design to this JCOG9812. The protocol involves initial review of radiation planning and final review of the actual radiation record for all randomized patients. The JCOG0301 was activated in September 2003, and we have achieved very good protocol compliance upto now.

Acknowledgments

We thank Ms M. Imai and Dr M. Niimi for their data management, and Dr H. Fukuda for his direction of the JCOG Data Center and oversight of management of the study. This study

was supported in part by Grants-in-Aid for Cancer Research (11S-2, 11S-4, 14S-2, 14S-4) and for Second Term Comprehensive 10-year Strategy for Cancer Control (H12-Gan-012) from the Ministry of Health, Labour and Welfare.

References

1. Annual Statistical Report of National Conditions. Tokyo: Health and Welfare Statistics Association 2002.
2. Choi NC, Doucette JA. Improved survival of patients with unresectable non-small cell bronchogenic carcinoma by an innovated high-dose en-bloc radiotherapeutic approach. *Cancer* 1981;48:101–9.
3. Perez CA, Pajak TF, Rubin P, Simpson JR, Mohiuddin M, Brady LW, et al. Long term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* 1987;59:1874–81.
4. Petrovich Z, Stanley K, Cox JD, Paig C. Radiotherapy in the management of locally advanced lung cancer of all cell types: final report of a randomized trial. *Cancer* 1981;48:1335–40.
5. Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med* 1990;323:940–5.
6. Gregor A, Macbeth FR, Paul J, Cram L, Hansen HH. Radical radiotherapy and chemotherapy in localized inoperable non-small-cell lung cancer: a randomized trial. *J Natl Cancer Inst* 1993;85:997–9.
7. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small-cell lung cancer: a randomized study. *J Clin Oncol* 1996;14:1065–70.
8. Johnson DH, Einhorn LH, Bartolucci A, Birch R, Omura G, Perez CA, et al. Thoracic radiation therapy dose not prolong survival in patients with locally advanced, unresectable non-small cell lung cancer. *Ann Intern Med* 1990;113:33–8.
9. Le Chevalier T, Arriagada R, Quoix E, Ruffie P, Martin M, Tarayre M, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. *J Natl Cancer Inst* 1991;83:417–23.
10. Schaake-Koning C, van den Bogaert W, Dalesio O, Festen J, Hoogenhout J, van Houtte P, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992;326:524–30.
11. Trovó MG, Minatel E, Franchin G, Boccieri MG, Nascimben O, Bolzicco G, et al. Radiotherapy versus radiotherapy enhanced by cisplatin in stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1992;24:11–5.
12. Marino P, Preatoni A, Cantoni A. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stage IIIa and IIIb nonsmall cell lung cancer. A meta-analysis. *Cancer* 1995;76:593–601.
13. Pritchard RS, Anthony SP. Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer. A meta-analysis. *Ann Intern Med* 1996;125:723–9.
14. Langer CJ, Hsu C, Curran WJ, Komaki R, Lee JS, Byhardt R, et al. Elderly patients with locally advanced non-small cell lung cancer (LA NSCLC) benefit from combined modality therapy, secondary analysis of radiation therapy oncology group (RTOG) 94-10. *Proc Am Soc Clin Oncol* 2002;21:299a (abstract).
15. Schild SE, Stella PJ, Geyer SM, Bonner JA, McGinnis WL, Mailliard JA, et al. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. *J Clin Oncol* 2003;21:3201–6.
16. Movsas B, Scott C, Sause W, Byhardt R, Komaki R, Cox J, et al. The benefit of treatment intensification is age and histology-dependent in patients with locally advanced non-small cell lung cancer (NSCLC): a quality-adjusted survival analysis of radiation therapy oncology group (RTOG) chemoradiation studies. *Int J Radiat Oncol Biol Phys* 1999;45:1143–9.
17. Sause W, Kolesar P, Taylor S IV, Johnson D, Livingston R, Komaki R, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer. Radiation therapy oncology group, Eastern cooperative oncology group, and Southwest oncology group. *Chest* 2000;117:358–64.
18. Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. *N Engl J Med* 1994;331:896–903.
19. Gomez H, Mas L, Casanova L, Pen DL, Santillana S, Valdivia S, et al. Elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy plus granulocyte–macrophage colony-stimulating factor: identification of two age subgroups with differing hematologic toxicity. *J Clin Oncol* 1998;16:2352–8.
20. Langer CJ, Manola J, Bernardo P, Kugler JW, Bonomi P, Cella D, et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. *J Natl Cancer Inst* 2002;94:173–81.
21. Kubota K, Fruse K, Kawahara M, Kodama N, Ogawara M, Takada M, et al. Ciplatin-based combination chemotherapy for elderly patients with non-small-cell lung cancer. *Cancer Chemother Pharmacol* 1997;40:469–74.
22. Calvert AH, Harland SJ, Newell DR, Siddik ZH, Jones AC, McElwain TJ, et al. Early clinical studies with cis-diammine 1,1-cyclobutane dicarboxylate platinum II. *Cancer Chemother Pharmacol* 1982;9:140–7.
23. Smith IE, Harland SJ, Robinson BA, Evans BD, Goodhart LC, Calvert AH, et al. Carboplatin: a very active new cisplatin analog in the treatment of small cell lung cancer. *Cancer Treat Rep* 1985;69:43–6.
24. Wiltshaw E. Ovarian trials at the Royal Marsden. *Cancer Treat Rev* 1985;12 (Suppl A):67–71.
25. Begg AC, van der Kolk PJ, Emondt J, Bartelink H. Radiosensitization *in vitro* by cis-diammine (1,1-cyclobutanedicarboxylato) platinum (II) (carboplatin, JM8) and ethlenediammine-malonato-platinum (II) (JM40). *Radiother Oncol* 1987;9:154–65.
26. Eisenberger M, Van Echo D, Aisner J. Carboplatin: the experience in head and neck cancer. *Semin Oncol* 1989;16 (Suppl 5):34–41.
27. Knox RJ, Friedlos F, Lydall DA, Roberts JJ. Mechanism of Cytotoxicity of anticancer platinum drugs: evidence that cis-diamminedichloroplatinum (II) and cis-diammine-(1,1-cyclobutanedicarboxylato) platinum (II) differ only in the kinetics of their interaction with DNA. *Cancer Res* 1986;46:1972–9.
28. O'Hara JA, Douple EB, Richmond RC. Enhancement of radiation-induced cell kill by platinum complexes (carboplatin and iproplatin) in V79 cells. *Int J Radiat Oncol Biol Phys* 1986;12:1419–22.
29. Atagi S, Kawahara M, Ogawara M, Matsui K, Masuda N, Kudoh S, et al. Phase II trial of daily low-dose carboplatin and thoracic radiotherapy in elderly patients with locally advanced non-small cell lung cancer. *Jpn J Clin Oncol* 2000;30:59–64.
30. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment, Vol. 48. WHO Offset Publication, Geneva: World Health Organization 1979.
31. Kaplan ES, Meier P. Non parametric estimation for incomplete observations. *J Am Stat Assoc* 1958;53:557–80.
32. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163–70.
33. Shoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometrics* 1982;38:163–70.
34. Ishikura S, Teshima T, Ikeda H, Hayakawa K, Hiraoka M, Atsgi S, et al. Initial experience of quality assurance in radiotherapy within the Japan Clinical Oncology Group (JCOG). *Radiother Oncol* 2002;64:S224.
35. Ohe Y, Yamamoto S, Suzuki K, Hojo F, Kakinuma R, Matsumoto T, et al. Risk factors of treatment-related death in chemotherapy and thoracic radiotherapy for lung cancer. *Eur J Cancer* 2001;37:54–63.

VOLUME 23 · NUMBER 6 · FEBRUARY 20 2005

JOURNAL OF CLINICAL ONCOLOGY 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

Noboru Yamamoto, Tomohide Tamura, Haruyasu Murakami, Tatsu Shimoyama, Hiroshi Nokihara, Yutaka Ueda, Ikuo Sekine, Hideo Kunitoh, Yuichiro Ohe, Tetsuro Kodama, Mikiko Shimizu, Kazuto Nishio, Naoki Ishizuka, and Nagahiro Saijo

From the Division of Internal Medicine, National Cancer Center Hospital; Pharmacology Division and Cancer Information and Epidemiology Division, National Cancer Center Research Institute, Tokyo, Japan.

Submitted November 7, 2003; accepted August 19, 2004.

Supported in part by a Grant-in-Aid for Cancer Research (9-25) from the Ministry of Health, Labor, and Welfare, Tokyo, Japan.

Presented in part at the 38th Annual Meeting of the American Society of Clinical Oncology, May 18-21, 2002, Orlando, FL.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Tomohide Tamura, MD, Division of Internal Medicine, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan; e-mail: ttamura@ncc.go.jp.

0732-183X/05/2306-1061/$20.00

DOI: 10.1200/JCO.2005.11.036

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.

J Clin Oncol 23:1061-1069. © 2005 by American Society of Clinical Oncology

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 α = .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%

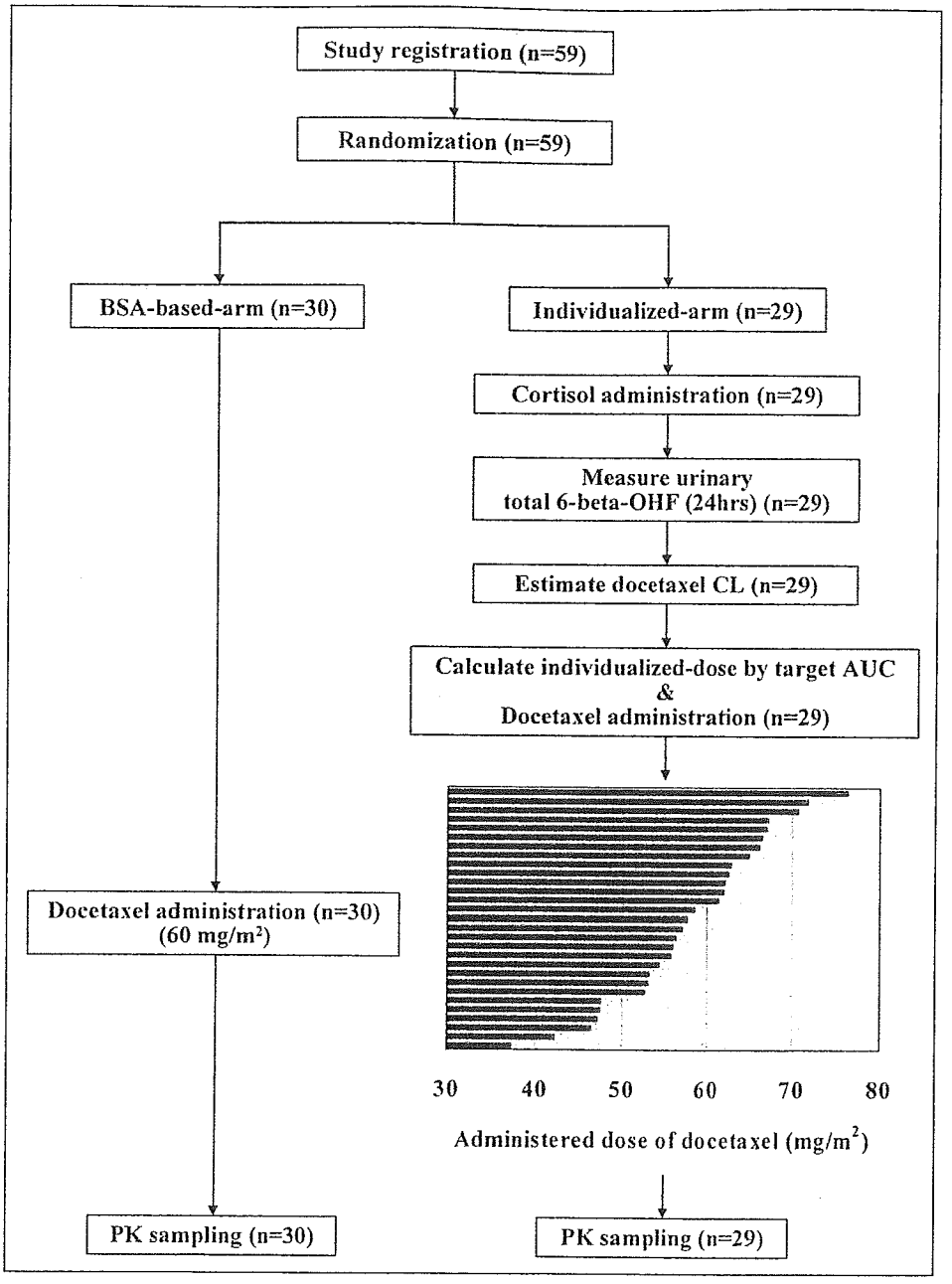


Fig 1. Study flow diagram and administered dose of docetaxel. PK, pharmacokinetic; AUC, area under the concentration-time curve; CL, clearance; 6-β-OHF, 6-beta-hydroxycortisol.

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

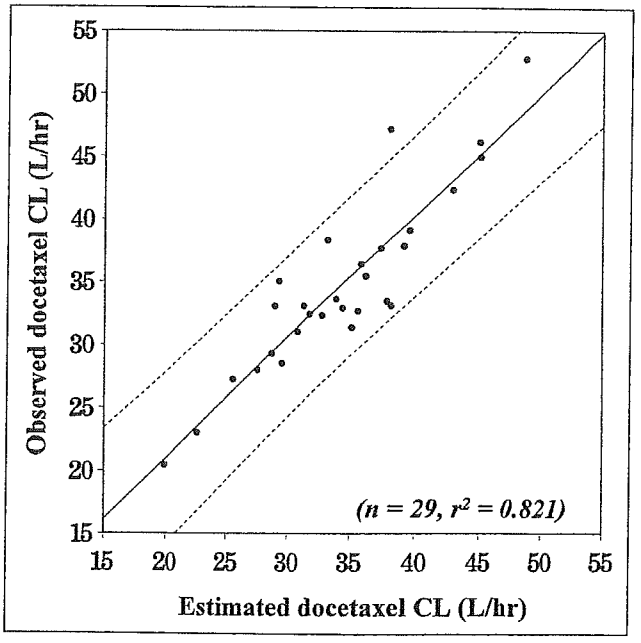


Fig 2. Correlation between the estimated and observed docetaxel clearance (CL) in the individualized arm (n = 29). (—) Linear regression line (r^2 = 0.821); (– – – –) 95% CIs for individual estimates.

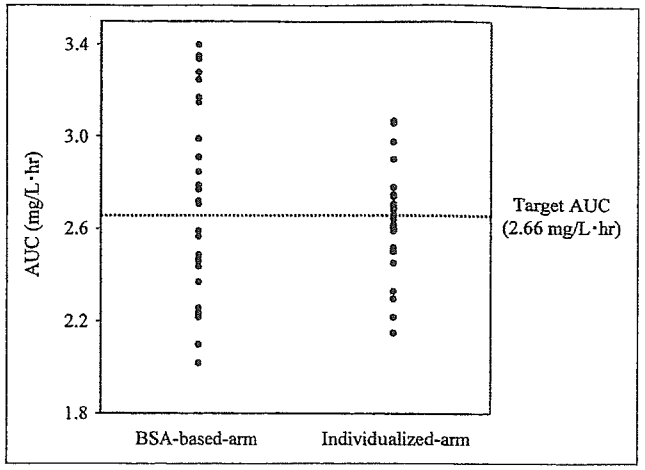


Fig 3. Comparison of area under the concentration-time curve (AUC) variability between the arms ($P < .01$; F test). BSA, body-surface area.

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.

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.

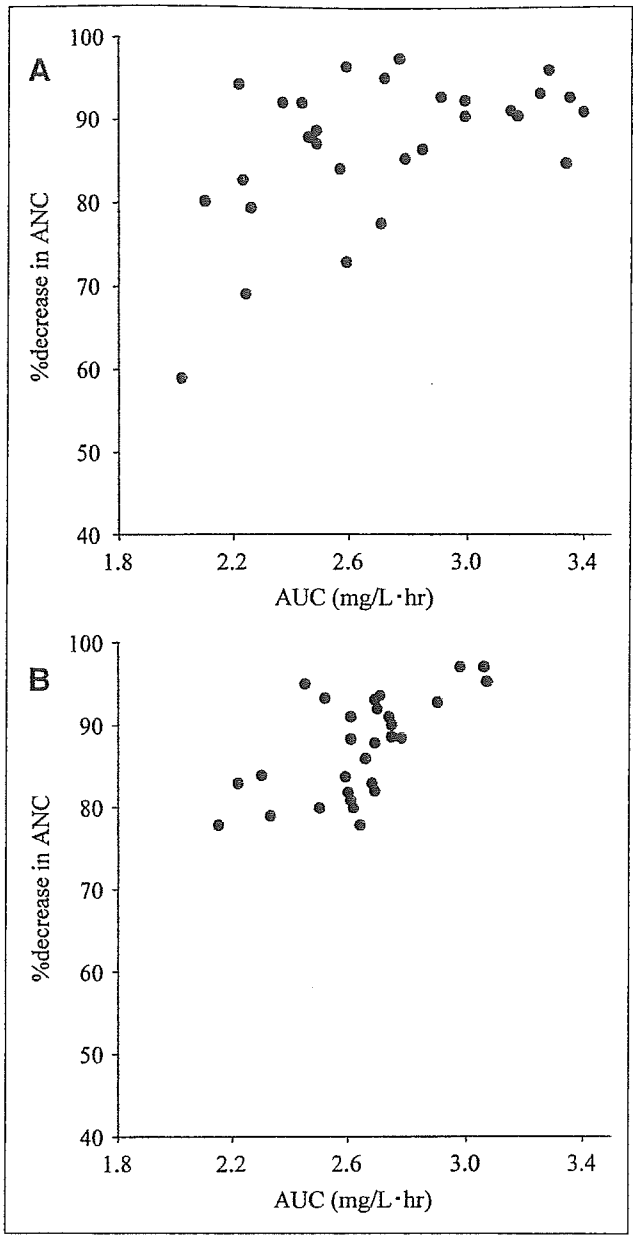


Fig 4. Correlation between area under the concentration-time curve (AUC) and percentage decrease in absolute neutrophil count (ANC) in each arm. (A) body-surface area–based arm; (B) individualized arm.

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).

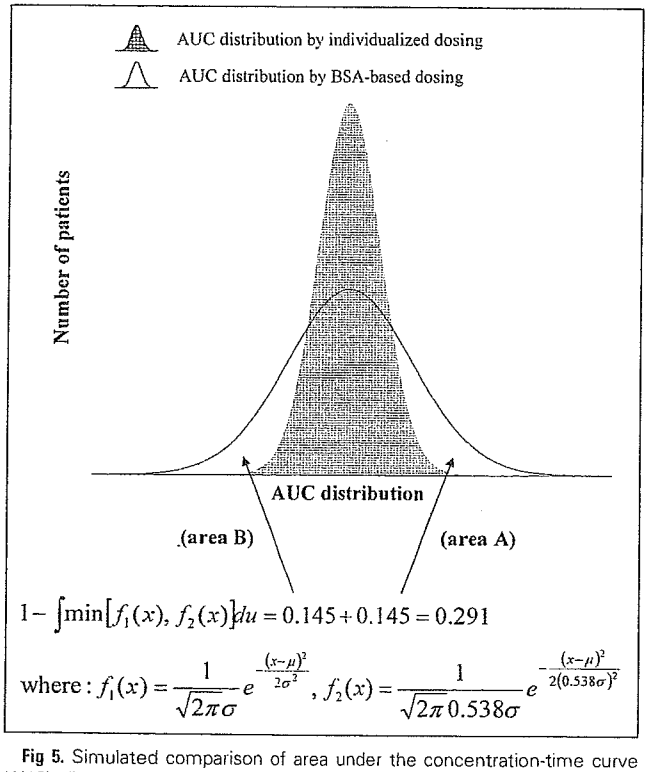


Fig 5. Simulated comparison of area under the concentration-time curve (AUC) distribution between body-surface area (BSA) –based dosing and individualized dosing when the variability of AUC is decreased 46.2% by individualized dosing applied using our method.

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

A Multicenter and Open Label Clinical Trial of Zoledronic Acid 4 mg in Patients with Hypercalcemia of Malignancy

Kenji Kawada, Hironobu Minami, Keniichi Okabe, Toru Watanabe, Keniichi Inoue, Morio Sawamura, Yasuo Yagi, Tsuneo Sasaki and Shigemitsu Takashima

Reprinted from **Japanese Journal of Clinical Oncology**, **Volume 35, No. 1** (2005) pp 28-33

Original article Published by Oxford University Press,
Great Clarendon Street, Oxford OX2 6DP, UK
Special.Sales@oupjournals.org
Tel: +44 (0) 1865 353827, Fax: +44 (0) 1865 353774
www.jjco.oupjournals.org

Jpn J Clin Oncol 2005;35(1)28–33
doi:10.1093/jjco/hyi005

A Multicenter and Open Label Clinical Trial of Zoledronic Acid 4 mg in Patients with Hypercalcemia of Malignancy

Kenji Kawada[1], Hironobu Minami[1], Keniichi Okabe[2], Toru Watanabe[3,9], Keniichi Inoue[4], Morio Sawamura[5], Yasuo Yagi[6], Tsuneo Sasaki[7] and Shigemitsu Takashima[8]

[1]Department of Oncology/Hematology, National Cancer Center Hospital East, Kashiwa, Chiba, [2]Department of Internal Medicine and [8]Department of Surgery, National Hospital Organization Shikoku Cancer Center, Matsuyama, [3]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, [4]Department of Breast Oncology, Saitama Cancer Center, Kitaadachi-gun, Saitama, [5]Department of Internal Medicine, National Hospital Organization Nishigunma National Hospital, Shibukawa, Gunma, [6]Department of Palliative Care Unit, Shakaihoken Kobe Central Hospital, Kobe and [7]Department of Chemotherapy, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

Received May 10, 2004; accepted October 19, 2004

Background: Hypercalcemia of malignancy is a serious complication of cancer. The objective of this study was to investigate the efficacy and safety of zoledronic acid, a new-generation bisphosphonate and the most potent inhibitor of bone resorption identified to date, for hypercalcemia of malignancy in Japanese patients.

Methods: Patients with hypercalcemia of malignancy, defined as an albumin-corrected serum calcium level ≥12.0 mg/dl, were treated with a single dose of zoledronic acid, 4 mg, by 15 min infusion. Clinical end-points included the proportion of patients with complete response, which was defined as a decrease of corrected serum calcium ≤10.8 mg/dl by day 10, and time to relapse, which is defined as the duration in days between the date of infusion and last available corrected serum calcium <11.6 mg/dl.

Results: Twenty-seven patients were enrolled in this study and 25 patients were evaluable for the efficacy of zoledronic acid. The mean corrected serum calcium level decreased from 14.5 to 9.6 mg/dl by day 10. The complete response rate was 84%. The median time to relapse was 23 days, ranging from 0 to 56 days. The most frequently observed adverse event was fever (≤38°C). Electrolyte abnormalities suspected to be drug related including grade 3 or 4 hypocalcemia, hypophosphatemia and hypokalemia were observed in 11 patients; however, all patients were asymptomatic. No serious adverse events associated with renal toxicity were reported.

Conclusions: Zoledronic acid is well tolerated and is effective for hypercalcemia of malignancy in Japanese patients.

Key words: bisphosphonate – hypercalcemia – zoledronic acid

INTRODUCTION

Hypercalcemia of malignancy (HCM) is among the most common and most serious complications of malignancy in the late stage. It occurs in 5–10% of all cancer patients at some point during the course of their disease, frequently in patients with cancer of the lung, breast, kidney, or head and neck, and adult T-cell leukemia. The early symptoms of HCM are mild and can be difficult to distinguish from symptoms of the underlying disease or the side effects of cancer therapy. If left untreated, it can progress rapidly and may become life-threatening. Patients who develop HCM generally have a short life expectancy, ranging from weeks to months (1). Treatment of HCM is important considering its life-threatening nature and symptoms such as anorexia, nausea, polyuria, confusion and coma.

Bisphosphonates are potent inhibitors of bone resorption and are the most effective therapy for HCM. Bisphosphonate compounds can be divided into two distinct pharmacological classes with different mechanisms of action depending on

For reprints and all correspondence: Hironobu Minami, Department of Oncology/Hematology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba, 277-8577 Japan.
E-mail: hminami@east.ncc.go.jp

[9]Present address: International University of Health and Welfare, 8-5-35 Akasaka, Minato, Tokyo, Japan

whether they contain a nitrogen atom in their side chains (2). Non-nitrogen-containing bisphosphonates, which are first-generation bisphosphonates, including etidronate and clodronate, are metabolized intracellularly to cytotoxic, non-hydrolyzable analogs of ATP that may inhibit ATP-dependent intracellular enzymes in osteoclasts (2). Nitrogen-containing bisphosphonates, which are second- or third-generation bisphosphonates including pamidronate, alendronate and ibandronate, inhibit protein prenylation, which leads to loss of membrane localization of small G proteins such as Ras, Rho and Rac. Consequently, osteoclasts may undergo apoptosis (2). They are more potent than the first-generation bisphosphonates and have been used for the treatment of HCM.

Zoledronic acid (ZOMETA; Novartis Pharmaceuticals Corporation, East Hanover, NJ) is a newer nitrogen-containing bisphosphonate that has been shown in preclinical studies to be more potent than currently available bisphosphonates including pamidronate. Zoledronic acid was 850-fold more effective than pamidronate in inhibiting the induction of hypercalcemia in rats, and 100-fold more potent than pamidronate in inhibiting calcium release in an *in vitro* calvaria assay (3).

Zoledronic acid at doses of 2, 4 and 8 mg/body was well tolerated in a phase 1 study for Japanese cancer patients with bone metastases (4). This phase 1 study also demonstrated that 4–8 mg of zoledronic acid was more effective with respect to suppressing markers of bone resorption than the lower dose, suggesting that these dose levels might be more potent to inhibit osteoclast activity.

For treating HCM, randomized, controlled clinical studies were conducted in the USA, Canada, Australia and European countries to compare the efficacy and safety of zoledronic acid and pamidronate (5). The complete response rate and time to relapse among patients treated with zoledronic acid 4 or 8 mg were superior to those among patients treated with pamidronate 90 mg, while maintaining a similar safety profile. Zoledronic acid at a single dose of 4 mg was nearly as effective as 8 mg, and the differences between the two doses were not statistically significant. Therefore, zoledronic acid at a single dose of 4 mg was recommended and has been approved for treatment of HCM in many countries since 2000.

A multicenter study was conducted to investigate the efficacy and safety of zoledronic acid in Japanese patients with HCM.

PATIENTS AND METHODS

This clinical study was conducted at seven hospitals in Japan between July 2001 and May 2002. The institutional review boards of the study hospitals approved the protocol. Written informed consent was obtained from each patient before participation in the study; however, if the patient was in a severe diminished state of consciousness due to HCM, written consent could be obtained from a relative such as the patient's spouse. In that case, the patient's informed consent to continue in the study was obtained after his/her level of consciousness was improved.

PATIENTS

Patients aged 20 years and older with histological or cytological confirmation of cancer and hypercalcemia, defined as an albumin-corrected serum calcium (CSC) $\geq$12.0 mg/dl, were eligible. The CSC was calculated by the following formula: CSC (mg/dl) = patient's measured serum calcium (mg/dl) + 0.8 × [mid-range serum albumin of each institutional laboratory standard (g/dl) – patient's measured albumin (g/dl)]. Patients who had a history of allergic reaction to bisphosphonates or who had been treated with bisphosphonates for HCM within 3 months of study entry were excluded, as were patients who exhibited serum creatinine >4.5 mg/dl or who were treated with calcitonin within 72 h of study entry. Patients who were treated with newly initiated antineoplastic cytotoxic chemotherapy or hormonal therapy 6 days before or 10 days after the initial administration of this study drug, or with any investigational drugs within 1 month of study entry were also excluded. Additional exclusion criteria were for patients who were severely dehydrated, could not tolerate intravenous hydration, or suffered from hyperparathyroidism, adrenal insufficiency, vitamin D intoxication, milk alkali syndrome, sarcoidosis or other granulomatous disease, or multiple endocrine neoplasia syndromes.

TREATMENT

Patients were treated with a single dose of 4 mg of zoledronic acid via a 15 min intravenous infusion followed by hydration with 500 ml of saline over 2 h. Then patients were followed-up for 56 days or until relapse defined as CSC $\geq$11.6 mg/dl. Patients who were refractory to the initial therapy or who relapsed within 56 days after the initial treatment could be re-treated with a single dose of 4 mg of zoledronic acid and followed-up for 28 days or until relapse.

ASSESSMENT OF SAFETY AND EFFICACY

Efficacy was assessed by the CSC level, which was measured on days 4, 7, 10, 14, 17, 21, 24 and 28, and weekly thereafter up to day 56. Efficacy was also assessed by improvement of the symptoms of HCM on days 4, 7, 10 and 56. The improvement of symptoms, i.e. depressed level of consciousness, anorexia, nausea, vomiting, fatigue and mouth dryness, was defined as an improvement in the grade as evaluated according to the National Cancer Institute's Common Toxicities Criteria version 2 in comparison with those before treatment.

Safety was evaluated by clinical findings, adverse events, vital signs, routine blood chemistries, hematological values and urinalysis. The severity of adverse events was graded according to the National Cancer Institute's Common Toxicities Criteria version 2.

STATISTICAL METHODS

The determination of the sample size was based on the proportion of patients achieving a complete response (CR), which

was defined as a decrease of CSC below 10.8 mg/dl by day 10, using Fleming's single-stage procedure. The CR rate representing a level of activity of definitive interest was considered to be 85% as expected from the efficacy of zoledronic acid 4 mg reported by Major et al. (5). A minimal threshold response rate was considered to be 60%, based on the CR rate of pamidronate 45 mg in three previous Japanese clinical trials for treatment of HCM (in-house data of Novartis). Thus, the required sample size was calculated to be 25, based on a hypothesis of an anticipated efficacy rate of 85%, threshold efficacy rate of 60%, alpha = 0.05 (two-sided) and beta = 0.2.

Primary analysis was based on the CR rate by day 10. The proportions of patients who achieved a CR by day 4 and/or day 7 were also evaluated. The change from baseline in CSC was also assessed at days 4, 7 and 10. For patients with missing CSC values, the last CSC observation available was carried forward. The time to relapse was defined as the number of days from the date of study drug infusion to the date of the last CSC <11.6 mg/dl. All patients who did not achieve a CR had their time to relapse set to zero and were not censored. Patients who died after a CR was achieved but before documentation of relapse were assumed to have relapsed on the day the last CSC was obtained. All other complete responders who discontinued or completed the study without documented relapse were censored on the last day on which CSC was obtained. Duration of CR was calculated using rules similar to time to relapse, except that the duration was based on the day of onset of the CR rather than the start date of the infusion. Duration of CR was calculated only for the subset of patients who had a CR. Time to relapse and duration of CR were estimated by the Kaplan–Meier method.

The impact of the baseline CSC ($\geq$13.6 or <13.6 mg/dl), with or without bone metastases, cancer type (breast/myeloma or other) and the parathyroid hormone-related protein (PTHrP, $\leq$2.0 or >2.0 pmol/l) on whether the patient achieved a CR was analyzed by Fisher's exact test. Log rank test was also used to analyze the impact of the above-mentioned demographic factors on the time to relapse.

RESULTS

Characteristics of the Patients

Twenty-seven patients were enrolled in the study and 26 patients were treated with zoledronic acid. One patient withdrew his consent before study drug infusion. Table 1 lists the characteristics of the treated patients. Half of the patients (13 out of 26) had a poor performance status of 3 or 4, and 24 patients had symptoms associated with HCM. Twenty-one out of 26 patients had an elevated (>2 pmol/l) PTHrP at baseline. As one patient died due to progressive disease without any CSC values after administration of the study drug, this subject could not be included in the efficacy analysis.

Table 1. Patient characteristics

No. of patients	26 (100%)
Gender	
Male	12 (46%)
Female	14 (54%)
Age (years)	
Mean ± SD	59.0 ± 9.8
Median	58.5
Range	37–75
Weight (kg)	
Mean ± SD	53.9 ± 12.2
Median	50.2
Range	37.6–85.7
ECOG PS	
0	0
1	9 (35%)
2	4 (15%)
3	8 (31%)
4	5 (19%)
Primary cancer site	
Lung	5 (19%)
Breast	8 (31%)
Multiple myeloma	3 (12%)
Head and neck	5 (19%)
Other	5 (15%)
Bone metastases (*n*, %)	
No	11 (42%)
Yes	15 (58%)
Symptom of hypercalcemia (*n*, %)	
No	2 (8%)
Yes	24 (92%)
PTHrP (pmol/l)	
Mean ± SD	10.2 ± 11.8
Median	4.4
Range	0.6–48.8
$\leq$2.0 pmol/l	5 (19%)
>2.0 pmol/l	21 (81%)
Baseline serum creatinine (mg/dl)	
Mean ± SD	0.9 ± 0.3
Median	0.9
Range	0.5–1.6
Baseline CSC (mg/dl)	
Mean ± SD	14.4 ± 1.8
Median	14.1
Range	12.4–18.4

ECOG PS, Eastern Cooperative Oncology Group performance status; PTHrP, parathyroid hormone-related protein; CSC, corrected serum calcium.

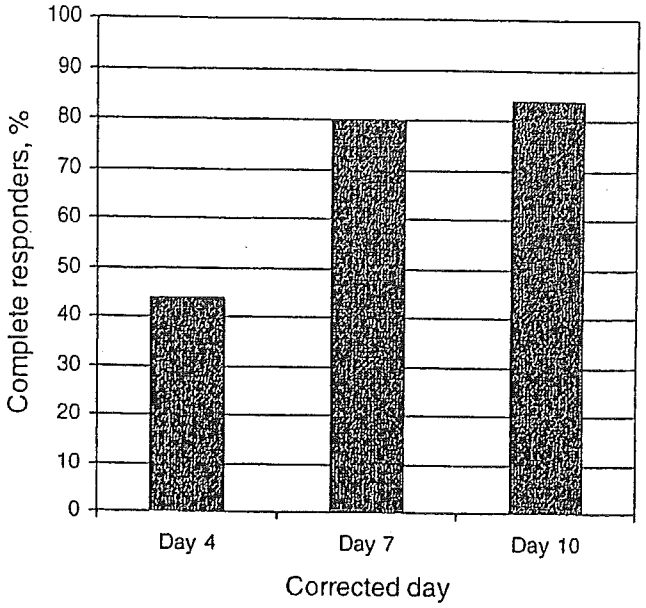


Figure 1. Percentage of patients achieving a CR (CSC ≤10.8 mg/dl). Days 4, 7 and 10 have a time window of days 2–5, 6–8 and 9–11, respectively.

CR Rate and Time to Relapse

The primary efficacy variable, CR rate by day 10, was 84% [95% confidence interval (CI), 63.9–95.5%] (Fig. 1). Approximately half of patients treated with zoledronic acid reached CR by day 4.

The CSC level decreased in all patients after zoledronic acid treatment (Fig. 2). Finally, four out of 25 patients did not achieve CR; however, their CSC levels decreased to ~11 mg/dl including a patient whose CSC was lowered by >5 mg/dl from baseline. The mean CSC level decreased from 14.5 mg/dl before treatment to 9.6 mg/dl on day 10. The mean (±SD) change in CSC level from day 1 (baseline) to days 4, 7 and 10 was −3.30 (±1.63), −4.67 (±1.84) and −4.89 mg/dl (±1.97), respectively.

The median time to relapse was 23 days, ranging from 0 (not CR) to 56 days (95% CI, 16–29 days). In patients who achieved CR, the median duration of CR was 22 days (95% CI, 11 to >56 days).

Efficacy According to Selected Subgroup

The CR rate and time to relapse were compared between patients with a baseline CSC of ≥13.6 or <13.6 mg/dl, with or without bone metastases, with breast/myeloma or other cancer types and with PTHrP ≤2.0 or >2.0 pmol/l (Table 2). Although there were only five patients with the lower value, there was a significant difference in time to relapse according to the baseline PTHrP ($P = 0.004$).

Clinical Symptoms Associated with HCM

Clinical symptoms associated with HCM, including depressed level of consciousness, anorexia, nausea, vomiting, fatigue

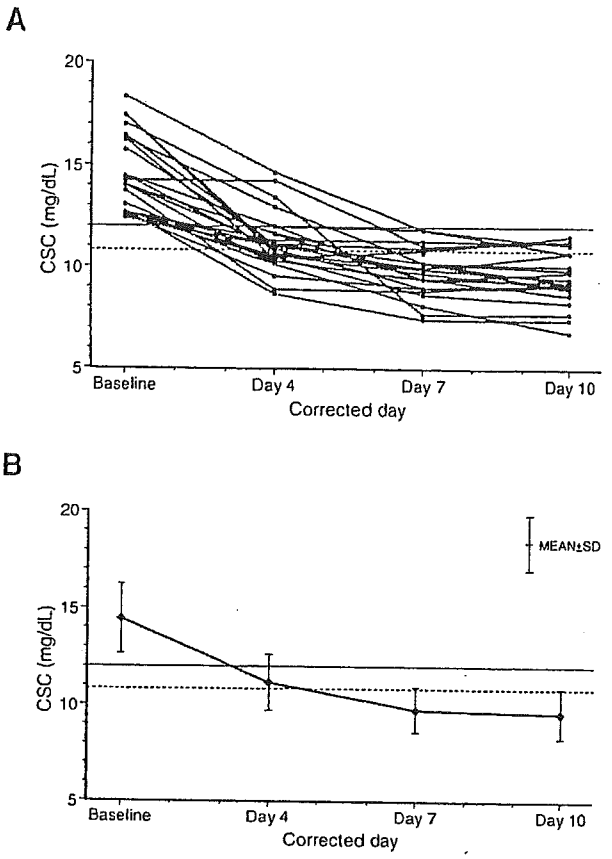


Figure 2. Course of the CSC in individual patients (A) and mean CSC (B) at baseline and days 4, 7 and 10 after treatment with zoledronic acid. Days 4, 7 and 10 have a time window of days 2–5, 6–8 and 9–11, respectively.

Table 2. CR rate and time to relapse of initial treatment for selected subgroup

	CR patients/ all patients	Median time to relapse in days (range)
All	21/25 (84%)	23 (0–56)
Baseline CSC		
≥13.6 mg/dl	13/16 (81%)	18 (0–56)
<13.6 mg/dl	8/9 (89%)	29 (0–56)
	$P = 1.00$	$P = 0.56$
Bone metastasis		
Present	14/15 (93%)	23 (0–56)
Absent	7/10 (70%)	22.5 (0–56)
	$P = 0.27$	$P = 0.90$
Cancer type		
Breast/myeloma	9/11 (82%)	28 (0–56)
Other	12/14 (86%)	17 (0–52)
	$P = 1.00$	$P = 0.33$
PTHrP level		
≤2.0 pmol/l	5/5 (100%)	>56 (10–56)
>2.0 pmol/l	16/20 (80%)	17 (0–52)
	$P = 0.55$	$P = 0.004$

Statistical data of CR rate and time to relapse were analyzed by Fisher's exact test and log rank test, respectively.