# Pharmacokinetics of Weekly Paclitaxel and Feasibility of Dexamethasone Taper in Japanese Patients with Advanced Non–small Cell Lung Cancer

Hiroshi Nokihara, MD, PhD[1]; Noboru Yamamoto, MD, PhD[1]; Yuichiro Ohe, MD, PhD[1]; Masaki Hiraoka, PhD[2,*]; and Tomohide Tamura, MD[1]

[1]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; and [2]Discovery Medicine & Clinical Pharmacology Japan, Bristol-Myers K.K., Tokyo, Japan

## ABSTRACT

**Purpose:** Weekly paclitaxel combined with a platinum-based agent has been advocated as an alternative regimen for patients with advanced non–small cell lung cancer (NSCLC). Limited studies exist on the tolerability of weekly paclitaxel in Japanese patients with advanced NSCLC. Furthermore, the feasibility of dexamethasone taper in the premedication regimen for weekly paclitaxel has not been examined in these patients. To address this issue, we assessed the maximum tolerated dose, dose-limiting toxicity, and pharmacokinetics of weekly paclitaxel in Japanese patients with advanced NSCLC in a dose-escalation Phase I trial and examined the feasibility of dexamethasone taper in these patients.

**Methods:** Weekly 1-hour infusions of paclitaxel were administered at doses of 80 to 120 mg/m$^2$ (dose escalation of 20 mg/m$^2$). The 7-week treatment cycle consisted of 6 infusions followed by a 2-week treatment interval. Pharmacokinetics were assessed during the first cycle. Dexamethasone was commenced at 16 mg and doses were successively halved if hypersensitivity reactions were absent.

**Findings:** A total of 15 patients with either Stage IIIB or IV NSCLC were enrolled. Although no dose-limiting toxicity was observed at 120 mg/m$^2$, 4 of 6 patients with peripheral neuropathy required discontinuation of treatment. The maximum accepted dose and the recommended dose were 120 and 100 mg/m$^2$, respectively. No grade $\geq 3$ adverse events were observed at 100 mg/m$^2$. The maximum drug concentration and AUC correlated with dose escalation. The pharmacokinetic parameters after the first and sixth infusions were similar, indicating that repeated administration of

paclitaxel did not result in drug accumulation or affect its pharmacokinetic profile. Partial response was observed in 3 of 15 patients. Plasma adrenocorticotropic hormone and cortisol levels decreased during treatment but approached baseline levels after a dexamethasone-free interval.

**Implications:** Weekly paclitaxel at 100 mg/m$^2$ given as a 1-hour infusion for 6 weeks followed by a 2-week treatment interval was well tolerated by Japanese patients with advanced NSCLC. Dexamethasone taper was feasible in these patients, and no clear trend in plasma adrenocorticotropic hormone or cortisol levels was observed. (*Clin Ther*. 2016;38:338–347) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

**Key words:** dexamethasone, paclitaxel, pharmacokinetics, phase I, safety.

## INTRODUCTION

The efficacy of paclitaxel in platinum-doublet regimens administered every 3 weeks as first-line treatment for advanced non–small cell lung cancer (NSCLC) is fully established.[1–5] Apart from the standard 3-weekly regimen, weekly paclitaxel combined with a platinum-based agent has been advocated as an alternative regimen for patients with advanced NSCLC.[6–9] This is based on the concept of dose-dense therapy, in which paclitaxel is administered at a relatively low dose but with more frequent (weekly)

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*M. Hiraoka has retired from Bristol-Myers K.K.

administration than the standard regimen. In theory, dose-dense therapy enables maintenance of therapeutic blood concentrations, thereby preventing the development of resistant tumor clones and tumor regrowth that potentially arise in the treatment-free intervals. Weekly paclitaxel has been demonstrated to be superior to standard 3-weekly regimens in advanced ovarian cancer[10] and metastatic breast cancer[11] and as adjuvant therapy for breast cancer.[12] In advanced NSCLC, similar efficacy was observed between weekly and 3-weekly paclitaxel regimens, but the former was associated with a significantly lower prevalence of arthralgia and grades 2 and 3 neuropathy.[9] Furthermore, weekly paclitaxel, either as combined or monotherapy, has been considered an active and feasible option in elderly patients in Phase II trials.[13,14] Limited studies exist on weekly paclitaxel in Japanese patients with advanced NSCLC.[13,15,16]

Despite premedication with dexamethasone and $H_1/H_2$ blockers, severe hypersensitivity reactions occur in 2% to 4% of patients receiving 3-weekly paclitaxel.[17] The standard premedication regimen is 20 mg of dexamethasone administered at 12 and 6 hours before paclitaxel infusions. This regimen repeatedly exposes patients to a potent, high-dose corticosteroid, particularly for those receiving weekly paclitaxel. Hypothalamic-pituitary-adrenal axis suppression is possible after prolonged dexamethasone administration, and abrupt cessation may cause adrenal insufficiency, although the risk for this in paclitaxel premedication regimens is unknown. To decrease the likelihood of dexamethasone-related adverse effects, attempts have been made to reduce the cumulative dose by reducing individual doses,[18] reducing frequency of administration,[19–24] tapering[25,26] or omission after uneventful completion of the first 1 or 2 paclitaxel doses.[17,27] The prevalence of hypersensitivity reactions after dexamethasone dose reduction in weekly paclitaxel regimens was comparable to that in those using routine premedication.[17,21,27] To our knowledge, no studies exist that have examined the feasibility of dexamethasone taper in Japanese NSCLC patients receiving weekly paclitaxel. Furthermore, there is little information about changes in adrenocortical function in patients receiving weekly dexamethasone as premedication for a weekly paclitaxel regimen.

The aims of the present study were to examine the pharmacokinetics, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) of weekly paclitaxel in Japanese patients with advanced NSCLC and to examine the feasibility of dexamethasone taper in the premedication regimen. The secondary objective was to investigate the effect of dexamethasone on adrenocortical function in Japanese NSCLC patients by analyzing plasma ACTH and serum/urinary cortisol levels.

## PATIENTS AND METHODS
### Patient Recruitment

The study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan. All patients provided written informed consent before enrollment in the study. Patients were eligible for the study if they met the following inclusion criteria: (1) a histologically or cytologically proven diagnosis of NSCLC; (2) age between 20 and ≤75 years; (3) an Eastern Cooperative Oncology Group Performance Status of 0 or 1; (4) an interval of at least 4 weeks since completion of prior treatment for NSCLC, and an interval of at least 2 weeks since completion of treatment with biological response modifiers, adjuvant therapy, or radiotherapy limited to the brain or bones; (5) a life expectancy of at least 2 months from the start of treatment; (6) ability to receive at least one treatment cycle as an inpatient; and (7) adequate organ function. The exclusion criteria were as follows: (1) history of paclitaxel therapy; (2) poorly controlled diabetes mellitus or presence of serious complications of diabetes; (3) history of serious hypersensitivity reaction or anaphylaxis; (4) history of hypersensitivity to preparations containing polyoxyethylene castor oil or hydrogenated castor oil; (5) presence of peripheral neuropathy grade ≥1 (National Cancer Institute Common Terminology Criteria for Adverse Events version 2.0); (6) presence of an acute inflammatory disease; (7) pregnancy or breastfeeding in women; and (8) patients for whom supportive therapy, such as life-saving blood transfusions for myelosuppression, was not possible.

### Premedication and Paclitaxel Administration

Dexamethasone at varying doses (1–16 mg IV) followed by diphenhydramine at 50 mg (oral) and ranitidine at 50 mg (IV) were given 30 to 60 minutes before paclitaxel administration. Paclitaxel dissolved in 250 mL of saline was administered by IV infusion

over a period of 1 hour (within 1.5 hours or less in principle). One 7-week cycle of treatment consisted of paclitaxel administered once a week for 6 consecutive weeks followed by a 2-week treatment-free interval. Patients received at least 1 cycle of treatment.

Dexamethasone was administered at an initial dose of 16 mg. In week 2, if there was no hypersensitivity reaction, it was subsequently administered at 8 mg. Successive doses were halved in the absence of hypersensitivity reactions to a minimal dose of 2 mg. If a hypersensitivity reaction occurred at 2 mg, the dose was increased to 4 mg in the following week of paclitaxel administration. If the MTD was determined, the initial dexamethasone dose of 8 mg, which was to be assessed for lower starting dose, could be tapered to a minimum of 1 mg in patients receiving the subsequently determined recommended dose, in the absence of hypersensitivity reactions.

Paclitaxel was administered at an initial dose of 80 mg/m$^2$ (level 1), and the dose was escalated in 20-mg/m$^2$ increments to a maximum of 160 mg/m$^2$ (level 5). Three patients were enrolled at each dose level. The next dose level was initiated if DLT was absent in all 3 patients. If a DLT occurred, 2 or 3 patients were added to the same dose level (3 + 3 design). If $\geq 2$ DLTs occurred in the group with a total of 5 or 6 patients at a dose level, the advice of the Data and Safety Monitoring Committee (DSMC) on the feasibility of a dose escalation was sought. The MTD was defined as the dose that caused $\geq 2$ DLTs in the original group of 3 patients or $\geq 3$ DLTs in the subsequent group of 5 or 6 patients.

DLTs were defined as the following events: (1) grade 4 leukopenia or thrombocytopenia; (2) grade 4 neutropenia lasting for $\geq 4$ days; (3) grade 3 leukopenia or neutropenia associated with a fever $\geq 38°C$; (4) grade $\geq 3$ nonhematologic toxicities (these were judged by the DSMC and excluded nausea/vomiting, anorexia, malaise, and toxicities attributable to the pathologic condition itself); and (5) toxicity leading to an omission of study treatment for $\geq 2$ weeks of the 6-week administration.

### Evaluations of Efficacy and Tolerability

Toxicities were evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events version 2.0. All signs and symptoms at baseline and those that appeared in the period from commencement of the first cycle to 2 weeks after completion

of treatment were documented. Tumor response was evaluated using Response Evaluation Criteria in Solid Tumors version 1.0.

### Pharmacokinetic Evaluation

Pharmacokinetic studies were conducted during the first cycle. Blood samples were collected from all patients immediately before and at 0, 0.5, 1, 2, 4, 7, 24, and 36 hours after infusion at weeks 1 and 6 and predose on day 15 or 22. The collected plasma was frozen until examination by HPLC.[28] The lower limit of quantitation of plasma paclitaxel was 0.020 μg/mL. The following pharmacokinetic parameters were calculated from the plasma concentration: $C_{max}$; $T_{max}$; $AUC_{0-\infty}$ obtained by linear/log-linear trapezoidal quadrature; $AUC0-\infty$ extrapolated by summing last quantified concentration/elimination rate constant to $AUC_{last}$; $AUC_{last}$; $t_{1/2}$ ($0.693/k_e$); $CL_{tot}$, total clearance (Dose/$AUC_{0-\infty}$); $MRT_{0-\infty}$, mean residence time ([area under the moment curve]/AUC); accumulation ratio (AUC [week 6]/AUC [week 1] or $C_{max}$ [week 6]/$C_{max}$ [week 1]); and $V_{ss}$, volume of distribution at steady state (CL × MRT). The mean (SD) of each pharmacokinetic parameter was calculated and tabulated by dose level and between the first and the final infusions in the first cycle. For each pharmacokinetic parameter, ANOVAs were tested between weeks 1 and 6 to identify pharmacokinetic changes during repeated administration.

### Measurement of Morning Plasma ACTH and Serum/Urinary Cortisol

Measurements of plasma adrenocorticotropic hormone (ACTH) and serum/urinary cortisol, as well as monitoring of adverse events, were conducted to assess the effect of dexamethasone on adrenocortical function. Weekly morning plasma ACTH and cortisol were measured during the first cycle of weekly paclitaxel treatment. Urinary cortisol and 6β-hydroxycortisol (OHC) in urine collected over 24 hours were measured at week 1 (day 1), week 3 (day 15), week 4 (day 22), and week 6 (day 36) in the first cycle, and before paclitaxel administration (day 50) in the second cycle. Examinations of plasma ACTH and serum/urinary cortisol were not performed in the second or subsequent cycles if no clinical abnormalities were seen during the first cycle. 6β-OHC levels were determined only in the first cycle. Mean (SD) urinary 6β-OHC/cortisol (C) ratios were

calculated before the start of paclitaxel infusion in weeks 1, 3, 4, and 6 of the first and second cycles.

## RESULTS

### Patient Characteristics

A total of 15 eligible patients with NSCLC were enrolled between October 2000 and July 2001, and their baseline characteristics are shown in Table I. All patients were male, with a median age of 57 years (range, 49–69 years), and 26.7% and 73.3% had an Eastern Cooperative Oncology Group Performance Status of 0 and 1, respectively. Of the 15 patients, 6 had prior surgical treatment, 3 had surgery plus radiotherapy, and 2 had chemotherapy only. Paclitaxel was initially given to 3, 3, and 6 patients at levels 1 (80 mg/m$^2$), 2 (100 mg/m$^2$), and 3 (120 mg/m$^2$), respectively. An additional 3 patients received paclitaxel at level 2 after obtaining the results of the level 3 dosing. All patients received at least 1 treatment cycle (median, 2; range, 1–5).

### Toxicity

No grade 4 toxicity was seen and no DLT occurred. Common toxicities at each respective dose level during the first cycle are listed in Table II. The most common adverse events were alopecia (93.3%), peripheral neuropathy (80%), anorexia (60%), fatigue (60%), and arthralgia (40%) during the first cycle. One patient had grade 1 Cushing syndrome during the fourth cycle while on 2 mg of dexamethasone. No grade ≥3 clinical nonhematologic malignancies were observed.

Peripheral neuropathy tended to worsen with the number of infusions. Higher doses were associated with earlier-onset and more severe peripheral neuropathy. Three patients, including 1 patient at level 2 and 2 patients at level 3, required omission of treatment during a cycle because of peripheral neuropathy. Apart from alopecia and peripheral neuropathy, routine treatment either resolved or mitigated most toxicities.

The most common hematologic and biochemical abnormalities were decreased red blood cell count (100%), hemoglobin (100%), and hematocrit (100%), followed by leukopenia (86.7%), neutropenia (66.7%), decreased serum albumin (66.7%), and elevated C-reactive protein (66.7%). Grade 3 leukopenia, neutropenia, and lymphocytopenia occurred in 13.3% of patients; all had received level 3 paclitaxel. All lymphocytopenias occurred in patients with grade 2 lymphocytopenia before paclitaxel treatment.

The MTD was not determined because no DLT occurred. DSMC identified hematologic toxicities of grade ≥3 and peripheral neuropathy that was associated with treatment discontinuation as DLTs. The maximum accepted dose was determined as level 3 because peripheral neuropathy necessitated treatment discontinuation during a treatment cycle in 4 of 6 patients in the level 3 cohort.

### Antitumor Activity

Of the 15 patients, 3 achieved a partial response, including 2 (of 6) at level 2 and 1 (of 6) at level 3. The

Table I. Patient characteristics (N = 15). Data are given as number of patients unless otherwise specified.

| Characteristic | | n |
|---|---|---|
| Sex | Male/female | 15/0 |
| Age, median (range), y | 57 (49–69) | 15 |
| ECOG performance status | 0 | 4 |
| | 1 | 11 |
| Histopathologic diagnosis | Adenocarcinoma | 9 |
| | Squamous cell carcinoma | 2 |
| | Large cell carcinoma | 1 |
| | NSCLC, not otherwise specified | 3 |
| Stage | IIIB | 3 |
| | IV | 12 |

ECOG = Eastern Cooperative Oncology Group; NSCLC = non–small cell lung cancer.

Table II. Common toxicities during the first cycle.

| Toxicity | 80 mg/m² (n = 3) | | | | 100 mg/m² (n = 6) | | | | 120 mg/m² (n = 6) | | | | All Levels | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 | G1 | G2 | G3 | G4 |
| Fatigue | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 4 | 1 | 0 | 0 | 8 | 1 | 0 | 0 |
| Anorexia | 2 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 6 | 0 | 0 | 0 |
| Arthralgia | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 6 | 0 | 0 | 0 |
| Peripheral neuropathy | 1 | 0 | 0 | 0 | 4 | 1 | 0 | 0 | 1 | 5 | 0 | 0 | 6 | 6 | 0 | 0 |
| Alopecia | 0 | 2 | 0 | 0 | 5 | 1 | 0 | 0 | 1 | 5 | 0 | 0 | 6 | 8 | 0 | 0 |
| Decreased hemoglobin | 3 | 0 | 0 | 0 | 5 | 1 | 0 | 0 | 5 | 1 | 0 | 0 | 13 | 2 | 0 | 0 |
| Decreased hematocrit | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Leukopenia | 1 | 0 | 0 | 0 | 4 | 2 | 0 | 0 | 1 | 3 | 2 | 0 | 6 | 5 | 2 | 0 |
| Neutropenia | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 1 | 3 | 2 | 0 | 3 | 5 | 2 | 0 |
| Lymphocytopenia | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 5 | 2 | 0 |
| Decreased serum albumin | 3 | – | – | – | 3 | – | – | – | 4 | – | – | – | 10 | – | – | – |
| Fasting hyperglycemia | 2 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 |

G = grade.

time period for confirmation of partial response ranged from 37 to 45 days. Seven patients achieved stable disease, and the overall response rate was 20.0%. Two patients showed progressive disease, and 3 patients had disease that was not evaluable.

### Pharmacokinetics

The pharmacokinetics of paclitaxel at weeks 1 and 6 in the first cycle are shown in Table III, and the plasma concentration–time profiles are illustrated in Figure 1. $C_{max}$ and $AUC_{0-\infty}$ increased proportionally with the increase in dose (Figure 2). Neither $t_{1/2}$ nor $V_{ss}$ exhibited dose dependency, but $CL_{tot}$ slightly decreased. Pharmacokinetic parameters and plasma paclitaxel concentration profiles were similar between the first and sixth infusions; the accumulation was not significant during repeated dosing.

### Plasma ACTH and Serum/Urinary Cortisol Levels

The administration of dexamethasone decreased morning plasma ACTH and cortisol levels by 9 to 14 pg/mL and 1.0 to 2.0 μg/dL, respectively. A 2-week dexamethasone-free interval was associated with levels that were similar to those at baseline (Table IV). Urinary 6β-OHC/C ratios after the first and sixth infusions were similar (Table V). The absence of a

change in the urinary 6β-OHC/C ratio suggested that cytochrome P-450 (CYP) 3A4 was unaffected by the administration of paclitaxel and dexamethasone.

### Dexamethasone Taper and Hypersensitivity Reactions

The prevalences of hypersensitivity reactions at dexamethasone doses of 16, 8, 4, and 2 mg were 8.3% (1 event of 12 infusions), 20% (3 of 15), 20% (3 of 15), and 14% (14 of 100), respectively. Dexamethasone dose reduction did not correlate with the prevalence of hypersensitivity reactions. In the group of 3 patients who received dexamethasone at 1 mg, none experienced a hypersensitivity reaction (0 events in 27 infusions). The hypersensitivity reactions were grade ≤2 and included hypotension, flushing, rash, malaise, and sinus bradycardia. The prevalence of hypersensitivity reaction did not correlate with the paclitaxel dose.

### DISCUSSION

The present Phase I study was conducted to examine the tolerability and pharmacokinetics of weekly paclitaxel in Japanese patients with advanced NSCLC, and the feasibility of dexamethasone taper for the premedication regimen. Our findings showed that no DLT

Table III.  Pharmacokinetic parameters. Data are given as mean (SD).

| Dose (mg/m²) | Infusion | $C_{max}$ (μg/mL) | P | $AUC_{0-\infty}$ (μg·h/mL) | P | $AUC_{last}$ (μg·h/mL) | P | $t_{½}$ (h) | P | $MRT_{0-\infty}$ (h) | P | $CL_{tot}$ (mL/min/m²) | P | (mL/min/body) | $V_{ss}$ (L/m²) | (L/body) | P | Rac |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 80 (n = 3) | Week 1 | 3.907 (0.383) | 0.8756 | 5.446 (0.451) | 0.9239 | 5.016 (0.390) | 0.9746 | 11.6 (1.3) | 0.6168 | 5.7 (1.3) | 0.5674 | 246.0 (20.7) | 0.9888 | 424.7 (61.8) | 83.7 (17.1) | 143.7 (27.8) | 0.6565 | 1.03 (0.22) |
|  | Week 6 | 4.061 (0.955) |  | 5.639 (1.479) |  | 5.156 (1.422) |  | 12.2 (1.5) |  | 6.2 (0.8) |  | 246.5 (58.2) |  | 426.1 (110.8) | 93.7 (31.8) | 161.6 (55.8) |  |  |
| 100 (n = 6) | Week 1 | 5.933 (0.760) | 0.9177 | 8.132 (1.544) | 0.8470 | 7.672 (1.484) | 0.9145 | 8.5 (2.4) | 0.0208 | 4.1 (1.1) | 0.0485 | 211.5 (41.6) | 0.9007 | 356.7 (82.2) | 50.0 (9.3) | 84.0 (17.0) | 0.0067 | 1.03 (0.13) |
|  | Week 6 | 5.904 (0.945) |  | 8.452 (2.291) |  | 7.899 (2.246) |  | 12.0 (1.9) |  | 5.9 (1.6) |  | 208.1 (49.1) |  | 350.4 (85.2) | 71.0 (11.9) | 118.4 (15.8) |  |  |
| 120 (n = 6) | Week 1 | 7.227 (0.898) | 0.0363 | 10.543 (1.056) | 0.0600 | 10.119 (0.931) | 0.0386 | 8.8 (2.8) | 0.1662 | 4.6 (1.9) | 0.2669 | 191.2 (17.7) | 0.0618 | 312.7 (31.7) | 52.4 (20.3) | 86.4 (36.7) | 0.0961 | 0.89 (0.06) |
| (n = 5) | Week 6 | 6.043 (0.549) |  | 9.059 (0.983) |  | 8.563 (0.981) |  | 12.4 (4.2) |  | 6.3 (2.3) |  | 222.9 (24.1) |  | 363.7 (47.8) | 83.0 (26.0) | 137.3 (49.5) |  |  |

*P values estimated by ANOVA for week 1 versus week 6.

$CL_{tot}$ = total clearance; $MRT_{0-\infty}$ = mean residence time; Rac = accumulation ratio; $V_{ss}$ = volume of distribution at steady state.
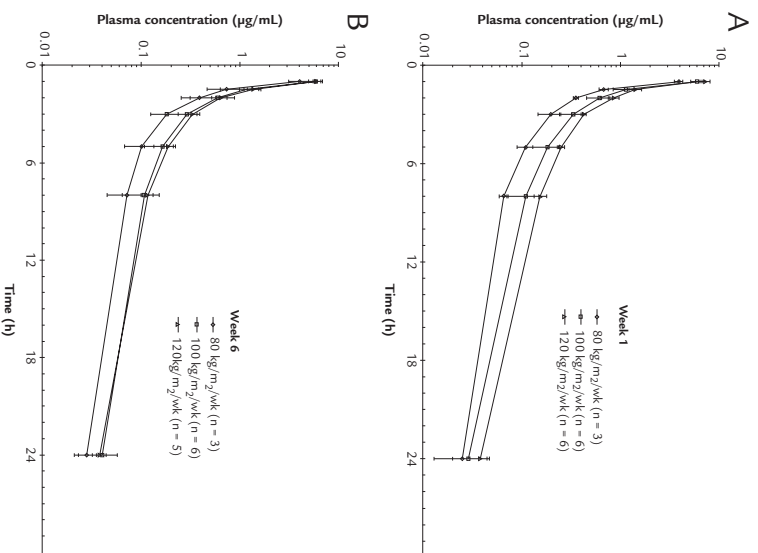


Figure 1. Changes in plasma paclitaxel concentrations after the first (A) and sixth (B) infusions.

occurred, and that maximum accepted dose and recommended dose were 120 and 100 mg/m², respectively.

Analysis of the adverse events in the 15 patients showed a safety profile comparable to those in other studies of weekly paclitaxel in advanced NSCLC.[6,13,15,16] Despite the relatively high prevalences of leukopenia and neutropenia, the severity was less than those in published studies of weekly paclitaxel for Japanese patients with NSCLC. In an early Phase II study of 3-weekly paclitaxel (210 mg/m²) in 60 Japanese patients with untreated Stage III to IV NSCLC, grade 4 neutropenia occurred in 30 patients (50%), with 17 patients requiring granulocyte colony-stimulating factor.[29] Subsequent studies of platinum-based agents with weekly paclitaxel at 40 to 70, 70, and 50 to 90 mg/m² in Japanese patients with advanced NSCLC showed that grade 3/4 neutropenia was also a relatively common adverse event, at 40%,[15] 70% (in patients aged ≥70 years),[13] and

Figure 2. Plots of $C_{max\ (A)}$ and $AUC_{0-\infty}$ (B) after the first infusion versus dose.
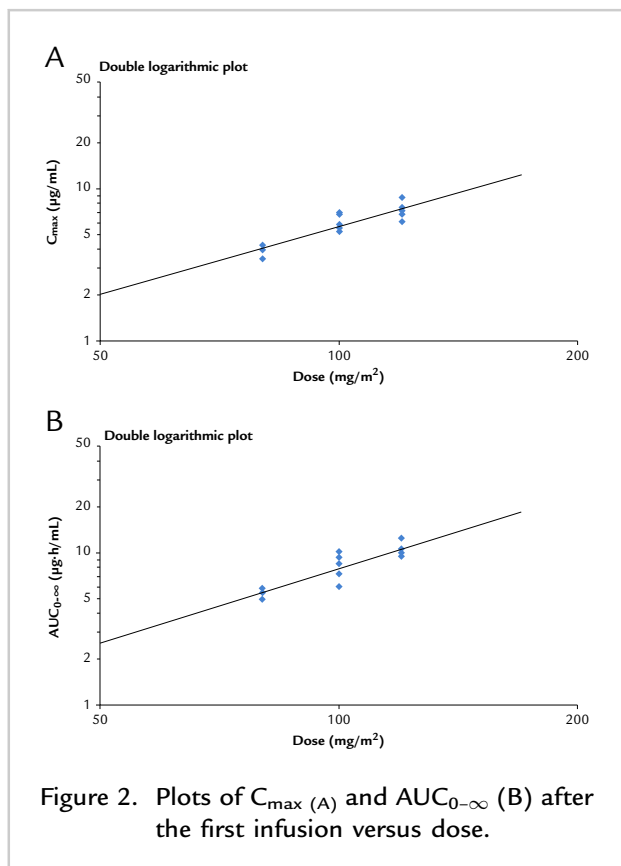
35%,[16] respectively. These prevalences of grade 3/4 neutropenia are comparable to that (39%) seen in non-Japanese patients with advanced NSCLC who received weekly paclitaxel at 150 mg/m$^2$.[6] Other notable hematologic toxicities in the present study

included anemia (100%; grade 3/4, 0%) and leukopenia (86.7%; grade 3/4, 20%), which are well-documented adverse effects of paclitaxel therapy. All nonhematologic adverse effects, apart from alopecia and peripheral neuropathy, either resolved or were mitigated with routine treatment. In the present study, peripheral neuropathy was relatively common (80%), but no cases were grade 3 or 4. Omission of paclitaxel during the cycle was required in 3 patients, whereas others had symptoms that were managed for 2 to 3 cycles (12–18 infusions).

Dexamethasone taper was conducted to reduce the likelihood of glucocorticoid-related adverse events in patients receiving weekly dexamethasone premedication before paclitaxel infusions. Adverse effects of excess glucocorticoid included Cushing syndrome (grade 1) in the fourth cycle (1 patient) and fasting hyperglycemia (7 patients; 5 patients with grade 1, and 2 patients with grade 2) between the first and fourth cycles. Dexamethasone dose reduction did not correlate with the prevalence of hypersensitivity reaction, and no severe hypersensitivity reactions occurred (all were grade ≤2). These observations are consistent with the lack of increase in the prevalence of significant hypersensitivity reactions in studies of lowered dexamethasone dose (10 mg) in patients on weekly paclitaxel regimens.[21,27] A recent report by Berger et al[17] described an absence of hypersensitivity reactions in 55 breast cancer patients whose dexamethasone premedication was ceased after uneventful first and second doses of paclitaxel, including 31 patients on weekly paclitaxel at 80 mg/m$^2$. To our knowledge, no

Table IV. Changes in plasma ACTH and cortisol. Samples were taken immediately before paclitaxel administration. Data are given as mean (SD).

| Cycle | Week | n | Plasma ACTH (pg/mL) | Plasma Cortisol (µg/dL) |
|---|---|---|---|---|
| 1 | 1 | 15 | 61.8 (23.1) | 17.01 (4.59) |
| | 2 | 15 | 48.2 (17.8) | 15.97 (5.16) |
| | 3 | 15 | 48.5 (23.8) | 15.49 (3.30) |
| | 4 | 15 | 47.8 (18.1) | 15.09 (3.40) |
| | 5 | 15 | 52.8 (22.3) | 15.70 (3.06) |
| | 6 | 15 | 48.3 (18.9) | 15.94 (3.90) |
| 2 | 1 | 11 | 71.2 (30.6) | 16.60 (3.34) |

ACTH = adrenocorticotropic hormone.

Table V. Urinary 6β-hydroxycortisol/cortisol ratio (OHC/C). Data are given as mean (SD).

| Timing of Urine Sampling | n | 6β-OHC/C |
|---|---|---|
| First cycle Week 1 | 15 | 6.999 (2.621) |
| Week 3 | 15 | 7.552 (3.095) |
| Week 4 | 15 | 7.565 (2.900) |
| Week 6 | 15 | 6.978 (2.073) |
| Before start of second cycle | 11 | 7.344 (2.675) |

study has attempted dexamethasone taper in Japanese NSCLC patients on a weekly paclitaxel regimen.

In the present study, plasma ACTH and serum/urinary cortisol were measured to examine the possible effect of dexamethasone premedication on adrenocortical function. Results showed that the administration of dexamethasone decreased morning plasma ACTH and cortisol levels by 9 to 14 pg/mL and 1.0 to 2.0 μg/dL, respectively, but levels approached those seen at baseline after a 2-week dexamethasone-free interval. No clear trend was observed in other static tests of adrenocortical function.

CYP3A4 is involved in the metabolism of paclitaxel, and its induction by paclitaxel has been demonstrated in vitro.[30] In the present study, urinary 6β-OHC/C ratios were determined to monitor paclitaxel-induced changes in CYP3A4 activity. The absence of a change in the urinary 6β-OHC/C ratio suggested that CYP3A4 was unaffected by the administration of paclitaxel and dexamethasone. This finding was consistent with the lack of correlation between plasma paclitaxel concentration and urinary 6β-OHC/C ratio in a study of patients with metastatic breast cancer on weekly paclitaxel.[31]

As listed in Table III, the PK characteristics at each dose of the 1-hour infusion in the present study were similar to those observed with a previous 3-hour infusion of 105 to 135 mg/m$^2$ of paclitaxel.[32]

Several study limitations warrant mention. The number of patients was small, and examination in a larger number of patients is needed. In particular, the reported rate[21] of severe hypersensitivity reactions due to paclitaxel is small (~2%), so the patient number in the present study was inadequate to observe a change in the prevalence of hypersensitivity reaction after dexamethasone taper. Second, only static tests of adrenocortical function were performed, and dynamic testing, specifically an ACTH stimulation test, is required to accurately assess adrenocortical function.

## CONCLUSIONS

Weekly infusions of paclitaxel at 100 mg/m$^2$ over 1 hour were well tolerated when administered in 6-week-long cycles followed by a 2-week treatment-free interval. Dexamethasone taper was found to be feasible for this weekly paclitaxel regimen and warrants further investigation. To our knowledge, this is the first study to evaluate weekly paclitaxel administration and the feasibility of dexamethasone tapering in Japanese patients with advanced NSCLC.

## CONFLICTS OF INTEREST

This study and the medical writing services used in compiling it were funded by Bristol-Myers K.K. M. Hiraoka was an employee of Bristol-Myers K.K. at the time of this study. H. Nokihara has received lecturer's fees from Boehringer Ingelheim, Eli Lilly,

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**Address correspondence to:** Hiroshi Nokihara, MD, PhD, Department of Thoracic Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: hnokihar@ncc.go.jp