after diagnosis with cisplatin-based chemotherapy [7]. In the 1990s, randomized trials using platinum in combination with new agents (vinorelbine and gemcitabine) have shown 1-year survival rates ranging between 36% and 39% [8,9]. However, many trials have failed to show a significant survival advantage of new compared with older combinations [10-12].

Docetaxel, a new agent, is a semisynthetic taxoid derived from the European yew *Taxus baccata* [13]. It is active against NSCLC and shows survival benefits not only in chemotherapy-naive patients, but also in those patients who have previously received platinum-based chemotherapy [14-21]. Phase II trials of docetaxel and platinum combinations have resulted in median survival rates ranging between 8.4 and 13.9 months, indicating that such combinations are active as first-line therapies [22-25]. Response rates of 30% to 67% for docetaxel with a platinum agent have also been demonstrated. Although docetaxel is usually administered as a 75 mg/m^2 dose, a phase II trial demonstrated that a response rate of 42% with an acceptable toxicity profile [26] could be achieved when 60 mg/m^2 of docetaxel and 80 mg/m^2 of cisplatin were administered to patients with stage IV NSCLC.

We conducted a randomized trial that compared docetaxel plus cisplatin (DC) with vindesine plus cisplatin (VdsC). The primary aim of this study was to compare the overall survival of stage IV NSCLC patients between the two regimens. Secondary end points included the response rate, duration of response, safety, and quality of life (QoL).

PATIENTS AND METHODS

Eligibility Criteria

This multicenter, randomized trial was conducted at 58 institutions in Japan between March 1998 and March 2000. Eligible patients were between the ages of 20 and 75 years, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; life expectancy $\geq$ 3 months; and previously untreated, stage IV, histologically or cytologically proven NSCLC with measurable lesions. Patients with PS of 3 because of pain from bone metastases were admitted to the study. Other eligibility criteria included leukocyte count $\geq$ 4,000/μL and $\leq$ 12,000/μL, neutrophil count $\geq$ 2,000/μL, platelet count $\geq$ 10^5/μL, hemoglobin $\geq$ 9.5 g/dL, blood urea nitrogen less than or equal to the upper limit of the institutional normal range (ULN), serum creatinine less than or equal to the ULN, creatinine clearance $\geq$ 60 mL/min, serum bilirubin less than or equal to the ULN, serum ALT and AST $\leq 2 \times$ ULN, and Pao_2 $\geq$ 70 mm Hg. Women who were pregnant or lactating were excluded from the study. Other exclusion criteria included patients with active infection, uncontrolled heart disease, interstitial pneumonia or active lung fibrosis, peripheral neuropathy, pleural or pericardial effusion that required drainage, past history of drug hypersensitivity, symptomatic brain metastasis, or active concomitant malignancy.

Patient eligibility was determined by the Patient Registration Center at the Tokyo Cooperative Oncology Group before patient registration. This study was approved by the institutional review boards at each participating center and all patients provided written informed consent.

Treatment Plan

Patients were randomly assigned to one of two treatment arms (Fig 1). In the experimental arm (DC), patients received docetaxel 60 mg/m^2 as a 1-hour intravenous infusion followed by cisplatin 80 mg/m^2 as a 2-hour infusion on day 1. Patients in the control arm (VdsC) received a bolus infusion of vindesine 3 mg/m^2 on days 1, 8, and 15, and cisplatin 80 mg/m^2 as a 2-hour infusion on day 1. Courses of treatment were repeated every 3 to 4 weeks in the DC arm, and once every 4 weeks in the VdsC arm.

Patients received at least two cycles of treatment unless disease progression or unacceptable toxicity was documented. Thereafter, responders or patients without disease progression continued treatment until the appearance of progressive disease or

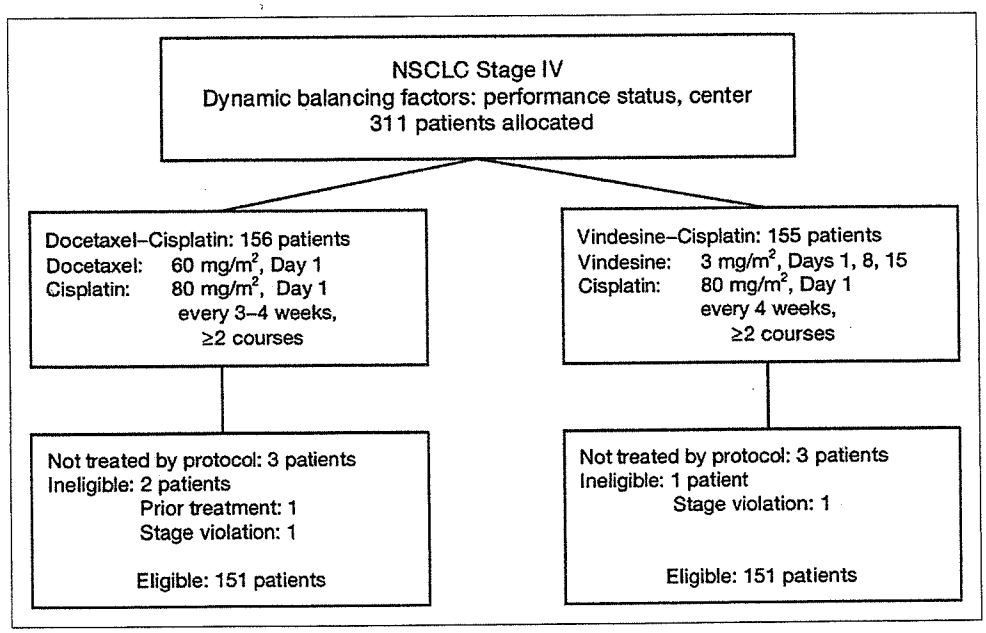

Fig 1. Study design and patient allocation. NSCLC, non–small-cell lung cancer.

a major toxicity. Because the efficacy of second-line docetaxel had not been established at the start of this study in 1998, cross-over administration of docetaxel and vindesine was prohibited in both treatment groups and the nature of second-line treatment was recorded.

No routine premedication was given for hypersensitivity reactions during the first cycle of treatment, although in subsequent cycles this was administered if a patient experienced a reaction. All hypersensitivity reactions were identified by the patient's physician and if deemed necessary, premedication drugs were administered by the investigator. However, recombinant human granulocyte colony-stimulating factor was administered when National Cancer Institute Common Toxicity Criteria grade 3 to 4 leukopenia or neutropenia occurred. If grade 4 neutropenia and/or leukopenia lasting for more than 3 days, grade 4 thrombocytopenia, grade 2 neuropathy, or grade 3 to 4 hepatotoxicity was observed, a 25% dose reduction of both drugs was implemented during the subsequent treatment cycle in both arms. If grade 3 stomatitis or renal toxicity occurred, the dose of cisplatin was reduced by 25%. Dose re-escalation was prohibited. Treatment was discontinued in the event of grade 3 neuropathy and again, dose re-escalation was prohibited. When leukocyte and platelet counts were less than 2,000/μL and 100,000/μL, respectively, or if infection developed at day 8 or 15, vindesine was withheld.

Patient Evaluation

Before chemotherapy, each patient underwent a complete medical history and physical examination, blood cell count determinations, biochemistry testing, chest x-ray, ECG, chest and whole-brain computed tomographic scan, abdominal ultrasound and/or computed tomographic scan, and isotope bone scan. Blood cell counts, differential WBC counts, and biochemistry testing were performed weekly during each course of chemotherapy.

Tumor responses were assessed radiographically and all responders were evaluated on extramural review. Treatment arms were blinded at the review. Standard WHO response criteria were used, and all responses were confirmed $\geq$ 28 days after initial documentation of the response.

QoL scores were measured using the validated instrument QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs developed in Japan [27]. The instrument consists of five domains (functional, physical, mental, psychosocial, and global), and it was completed by the patient before treatment began, before the second and third therapy cycles, and 3 months after the last cycle of treatment. Evaluations were not only performed during the course of treatment but also 2 years after study treatment.

Statistical Considerations

Survival from the date of enrollment was the primary end point. The sample size was chosen on the basis of a log-rank test used to compare the two randomized groups. A sample size of 150 patients per group was estimated on the basis of a projected median survival of 42 weeks in the DC group and 30 weeks in the VdsC group, with an α level of 5% (two sided) and a power of 80% to compare both groups. Dynamic balancing factors (ie, prerandomization stratification factors) included ECOG PS and institutions, and these were used to minimize any imbalance in treatment assignment.

Secondary end points included objective tumor response, response duration, rate of adverse drug reactions, and changes in QoL. The survival time and response duration were estimated for each group using the Kaplan-Meier method [28]. Response duration was calculated from the first date of a 50% reduction in the tumor to the last date that tumor reduction was documented. The difference in response duration was evaluated using the generalized Wilcoxon test. Tumor responses in both groups were compared using Fisher's exact test. Other categoric data, such as treatment data and the incidence of adverse events, were compared between treatment groups using the χ^2 test. QoL analyses were performed using repeated-measures analysis of variance between treatment groups on data collected before the second and third treatment cycles, and 3 months after the last cycle of treatment, adjusting for baseline QoL values.

An interim analysis on the basis of overall survival was planned for 1 year after enrollment of the last patient. The predefined early-stopping rule was based on a two-sided significance level of 0.005. The DeMets and Lan method was applied for multiple comparisons [29]. The analysis was monitored by the Independent Data Monitoring Committee. The final analysis was conducted 2 years after enrollment of the last patient and the final significance level was maintained at 0.0491.

RESULTS

Patient Characteristics

From April 1998 to March 2000, 311 previously untreated patients from 58 institutions were randomly assigned to treatment in the trial (Fig 1). However, six patients did not receive any protocol treatment (three in the DC arm and three in the VdsC arm). In the DC arm, one patient withdrew informed consent, another experienced a rapid increase in serum bilirubin beyond levels acceptable for inclusion into the study, and the third patient had an accident causing a thoracic spine pressure fracture; all withdrawals occurred before the first cycle of treatment. Likewise, before the first cycle of treatment, one patient in the VdsC arm had superior vena cava syndrome, one patient contracted pneumonia and the investigator decided against this patient receiving protocol treatment, and one patient (who also had pneumonia) had brain metastases and was therefore excluded from the study. An additional three patients failed to fulfill the eligibility criteria for the following reasons: stage violations (two patients, one per treatment arm) and prior treatment (one patient, DC arm). Because nine patients were deemed ineligible, 302 patients were evaluated—151 in each arm. All 302 patients were evaluated for survival, response, and toxicity. The characteristics of eligible patients are listed in Table 1.

Treatment Delivery

The median number of cycles was three for the DC arm and two for the VdsC arm ($P < .01$; Table 2). One hundred thirty-two patients (87%) in the DC arm and 115 patients (76%) in the VdsC arm received at least two cycles of chemotherapy. The reasons for terminating chemotherapy before the second treatment cycle in the DC and VdsC arms, respectively, were disease progression (7% v 13%), adverse events (5% v 6%), patient refusal (0% v 2%), and adverse event with patient refusal (1% v 3%).

Table 1. Patient Characteristics

Characteristic	Treatment Group DC (n = 151)	VdsC (n = 151)
Age, years		
Median	63	64
Range	30–74	39–74
Sex, No. of Patients		
Male	97	103
Female	54	48
Histology, No. of patients		
Adenocarcinoma	120	103
Squamous cell	17	33
Large cell	9	11
Adenosquamous	0	2
Other	5	2
ECOG performance status, No. of patients		
0	46	41
1	99	105
2	5	4
3	1	1

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin; ECOG, Eastern Cooperative Oncology Group.

Table 3. Treatment Outcomes

Outcome	Treatment Group DC (n = 151)	VdsC (n = 151)	P
Tumor response, No. of patients			
Complete	3	0	
Partial	53	32	
No change	63	76	
Progressive disease	27	38	
Not assessable	5	5	
Overall response rate, %	37.1	21.2	< .01
95% CI	29.4 to 45.3	15.0 to 28.6	
Median duration of response, weeks	10.0	8.4	.02
Survival			
Median, months	11.3	9.6	.014
95% CI	10.2 to 13.1	8.4 to 11.4	
1 year, %	47.7	41.4	
95% CI	39.7 to 55.6	33.5 to 49.3	
2 year, %	24.4	12.3	
95% CI	17.5 to 31.2	7.0 to 17.6	

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.

Response

Patients receiving DC had a significantly higher overall response rate than those receiving VdsC ($P = .0035$; Table 3). There were three complete responses and 53 partial responses, with an overall response rate of 37.1% (95% CI, 29.4% to 45.3%) in the DC arm. The VdsC arm resulted in 32 partial responses, with an overall response rate of 21.2% (95% CI, 15.0% to 28.6%). The median duration of response was 10.0 weeks in the DC arm versus 8.4 weeks in the VdsC arm ($P \doteq .20$).

Survival

The median survival time, 11.3 months (95% CI, 10.2 to 13.1 months) for the DC arm, was significantly greater than the 9.6-month (95% CI, 8.4 to 11.4 months) median survival of the VdsC arm (log-rank test, $P = .014$; Fig 2). The 1- and 2-year survival rates were 47.7% (95% CI, 39.7% to 55.6%) and 24.4% (95% CI, 17.5% to 31.2%) for the DC group, and 41.4% (95% CI, 33.5% to 49.3%) and 12.3% (95% CI, 7.0% to 17.6%) for the VdsC group, respectively (Fig 2).

Table 2. Treatment Delivery

Cycle of Treatment	Received Cycle of Treatment DC (n = 151) No. of Patients	%	VdsC (n = 151) No. of Patients	%
1	151	100	151	100
2	132	87	115	76
3	84	56	53	35
4	41	27	17	11
5	6	4	1	1
6	2	1	0	0
No. of cycles*				
Median	3		2	
Range	1–9		1–5	

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.
*$P = .01$.

Toxicity

National Cancer Institute Common Toxicity Criteria grade 3 and 4 hematologic toxicities, anemia, and leukopenia were significantly more severe among patients receiving VdsC compared with those receiving DC ($P < .01$; Table 4). Grade 4 neutropenia also occurred more frequently in the VdsC regimen (50.3%) than in the DC regimen (35.1%), but grade 3 or 4 thrombocytopenia was rare in both arms.

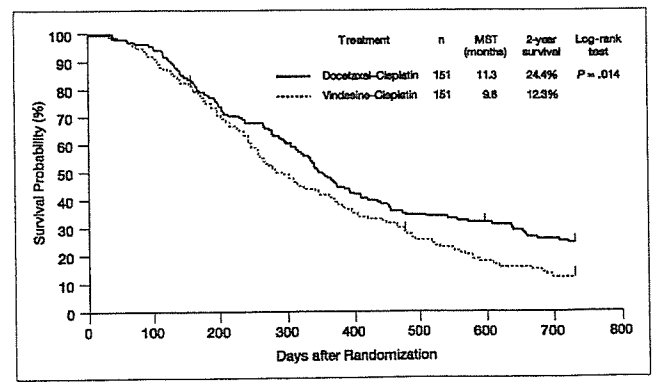

Fig 2. Kaplan-Meier survival estimates for patients treated with docetaxel plus cisplatin and patients treated with vindesine plus cisplatin. MST, median survival time.

Table 4. Grade 3 or 4 Hematologic Toxicities

Toxicity (grade)	Treatment Group: DC (n = 151) No. of Patients	%	VdsC (n = 151) No. of Patients	%	P
Anemia					< .01
3	15	10	34	23	
4	0		0		
Thrombocytopenia					
3	1	1	0	0	
4	0		0		
Leukopenia					< .01
3	66	46	92	68	
4	3		10		
Neutropenia					
3	59	74	41	77	
4	53		76		

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.

Table 6. Poststudy Treatment

Therapy	Treatment Group (% of patients): DC (n = 151)	VdsC (n = 151)
Chemotherapy	52	46
Platinum	29	23
Gemcitabine	26	19
Vinorelbine	15	15
Irinotecan	9	7
Paclitaxel	8	11
Gefitinib	3	1
Other	11	12
Docetaxel	23	5
Vindesine	0	7
Radiation	51	48
Surgery	2	2

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.

Grade 3 and 4 nonhematologic toxicities are listed in Table 5. The incidences of the majority of grade 3 or 4 nonhematologic toxicities were similar in both arms, with no significant differences between treatments. However, the incidences of grade 3 or 4 nausea and vomiting, anorexia, and diarrhea were significantly more frequent in the DC arm compared with the VdsC arm ($P < .05$, $P < .01$, and $P < .01$, respectively). There were two deaths in the DC arm that probably were related to treatment. One patient had acute myocardial infarction and died on day 2 of the first cycle of treatment; the second patient had obstructive pneumonia in the same lobe as the primary tumor and died on day 25 of the first course of therapy.

Table 5. Grade 3 or 4 Nonhematologic Toxicities*

Toxicity (grade)	Treatment Group: DC (n = 151) No. of Patients	%	VdsC (n = 151) No. of Patients	%	P
Nausea and vomiting					< .05
3	13	9	7	5	
4	0		0		
Anorexia					< .01
3	30	21	14	9	
4	1		0		
Diarrhea					< .01
3	6	9	2	1	
4	8		0		
Malaise					
3	6	4	3	3	
4	0		1		
Dysrhythmia					
3	3	2	2	1	
4	0		0		
AST elevation					
3	0		3	2	
4	0		0		
ALT elevation					
3	2	1	4	3	
4	0		0		
Bilirubin					
3	3	2	3	2	
4	0		0		

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.
*Occurring in ≥ 2% patients in at least one arm.

Poststudy Treatment

A total of 52% of patients receiving DC and 46% of patients receiving VdsC also received second-line chemotherapy. The agents used as second-line therapy in both arms were similar without usage of docetaxel and vindesine. Although cross-over treatments were considered to be protocol deviations, 5% of patients receiving first-line vindesine received second-line docetaxel, and these patients were included in survival analyses. Palliative radiotherapy was used in 51% of patients in the DC arm and 48% of patients in the VdsC arm (Table 6).

QoL

QoL questionnaires were completed at baseline, before the second and third treatment cycles, and 3 months after the last cycle of treatment by 82.1%, 83.1%, 76.6%, and 54.9% of patients in the DC arm (n = 151) and 82.8%, 89.6%, 61.6%, and 55.4% of patients in the VdsC arm (n = 151), respectively. Least squares mean scale values for the functional, physical, and mental domains tended to improve among patients receiving DC, but the difference only achieved statistical significance for the functional (nonphysical) domain ($P = .02$; Fig 3). A separate, more detailed analysis of QoL data currently is ongoing.

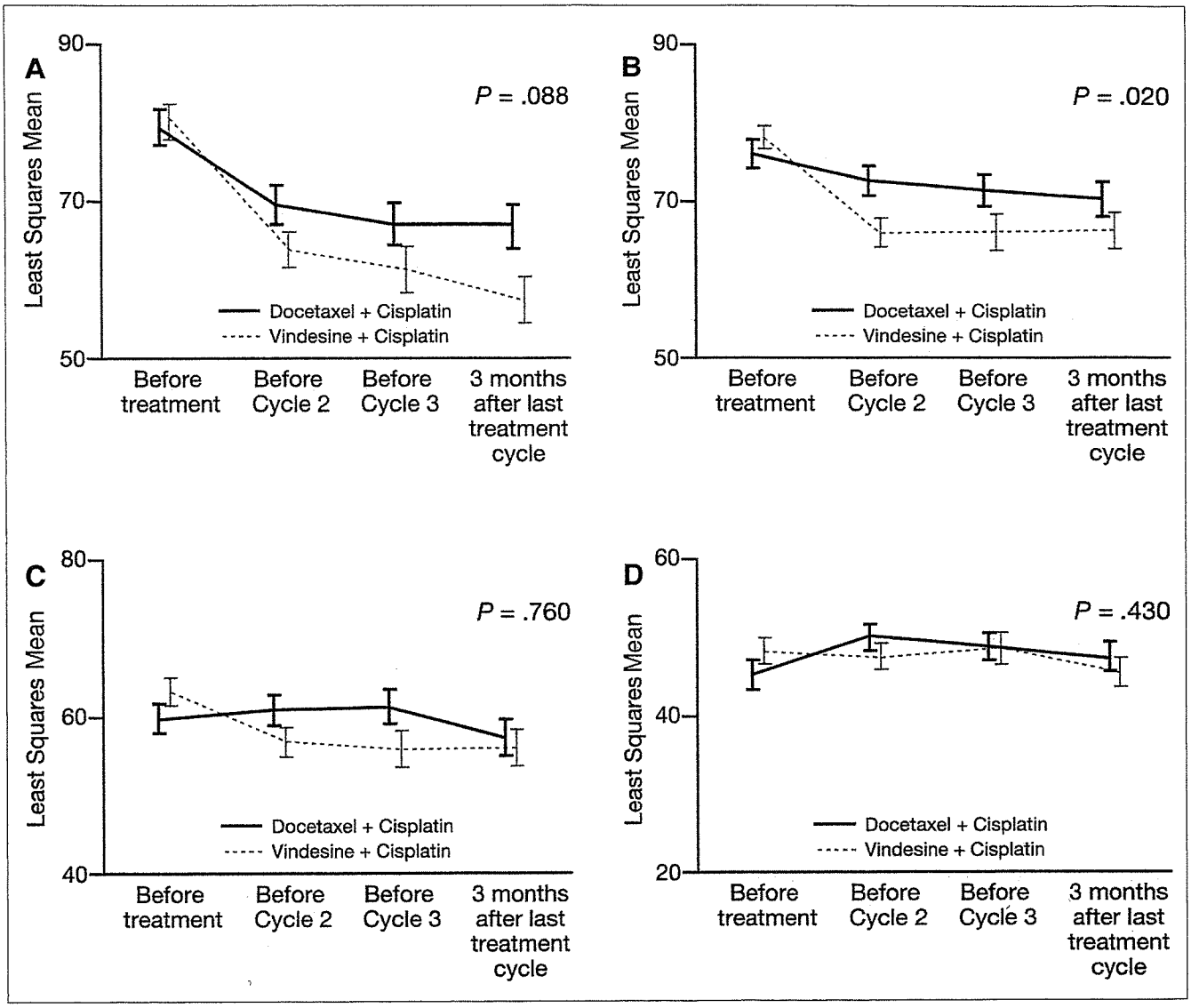

Fig 3. Quality-of-life assessments across four domains of the Quality of Life Questionnaire for Cancer Patients Treated with Anticancer Drugs instrument, among patients treated with docetaxel plus cisplatin and vindesine plus cisplatin. (A) Functional; (B) physical; (C) mental; and (D) psychosocial. Vertical bars represent least square means ± SE. Higher score indicates better quality of life.

DISCUSSION

Platinum-based combination chemotherapy is the treatment of choice for stage IV NSCLC patients with good performance status. The Big Lung Trial recently conducted in England confirmed the survival advantage of platinum-based combination chemotherapy in this setting [30]. The results of the present multicenter randomized trial reveal a significant survival advantage for DC when compared with VdsC in the treatment of patients with stage IV NSCLC. It is noteworthy that the 2-year survival rate in the DC arm was 24.3%—double that observed in the control arm. This is comparable to results for patients with stage III NSCLC who were treated with sequential chemoradiotherapy [4].

VdsC was chosen as the control arm because this regimen showed significant survival advantage over BSC in a Canadian trial [31]. In addition, this combination has long been the standard regimen for advanced NSCLC [22,31,32]. For instance, two randomized trials conducted in Japan, which compared the more recently developed agent irinotecan plus cisplatin with VdsC, failed to show an overall survival advantage for the irinotecan-containing regimen in advanced NSCLC [33,34]. In the European study, 612 patients were randomly assigned to receive vinorelbine plus cisplatin, vindesine plus cisplatin, or vinorelbine alone. In this study, the unadjusted log-rank test comparing the survival of patients who received vinorelbine plus cisplatin versus VdsC yielded a *P* value of .085 in favor of vinorelbine

plus cisplatin. Patients with both stage III and local recurrence (41%), or metastatic NSCLC (59%) were included, and nearly half of the patients received thoracic irradiation after chemotherapy [22]. The treatment strategy of locally advanced NSCLC is different from that of metastatic disease. Thus, the advantage of vinorelbine plus cisplatin over VdsC in patients with stage IV NSCLC has not been clearly defined.

Despite undergoing more treatment cycles, fewer patients on the DC arm experienced severe hematologic toxicities (including anemia and leukopenia) than patients treated with VdsC. Although diarrhea, nausea and vomiting, and anorexia were more frequently observed in the DC arm, such toxicities were easily managed with standard care.

DC has been evaluated in other phase III trials. In the ECOG trial, 1,207 patients were randomly assigned to paclitaxel plus cisplatin, gemcitabine plus cisplatin, docetaxel plus cisplatin, or paclitaxel plus carboplatin [35]. The response rate and median survival were similar among the four regimens for eligible patients at 19% and 7.9 months, respectively. In a large international trial (TAX-326), 1,218 chemotherapy-naive patients were randomly assigned to docetaxel plus cisplatin, docetaxel plus carboplatin, or vinorelbine plus cisplatin [36]. The DC arm favored a longer median survival time compared with the vinorelbine plus cisplatin arm (11.3 *v* 10.1 months) and response (31.6% *v* 24.5%). Although we must be careful when making retrospective comparisons, both survival figures and response data of the present study and TAX-326 were virtually identical and were better than those of the ECOG trial [35]. It is suggested that patients with more favorable prognostic factors entered in TAX-326 and the current study.

More recently, attention has focused on improving QoL as a goal of therapy for patients with advanced NSCLC [37]. One trial of docetaxel as second-line therapy versus BSC showed that chemotherapy resulted in significantly better control of pain and fatigue than did BSC [20]. In a similar comparative phase III trial, docetaxel, administered as first-line in chemotherapy-naive patients, was significantly better than BSC in controlling not only pain but also dyspnea and emotional functioning [19]. In the present study, QoL measures demonstrated that the physical domain was significantly better in the DC arm over the VdsC arm ($P = .020$). This finding of a QoL benefit with a docetaxel plus platinum combination is also supported by the results of TAX-326 [38]. This investigation indicated that patients in receipt of a docetaxel plus platinum combination reported greater global QoL benefit in terms of patient pain or less Karnofsky performance status deterioration than patients receiving vinorelbine plus cisplatin when the EuroQol and Lung Cancer Symptom Scale instruments were used [39,40].

In this study, we used 60 mg/m^2 of docetaxel on the basis of the phase II study conducted in Japan [26]. The dose of docetaxel is lower than the doses used in ECOG1594 and TAX-326 (docetaxel and cisplatin 75 mg/m^2) [35,36]. In a randomized trial comparing docetaxel alone with BSC in patients previously treated with platinum-based chemotherapy, docetaxel 100 mg/m^2 was not tolerated but docetaxel 75 mg/m^2 demonstrated significant survival benefit [20]. Therapeutic index was also better for the lower dose of docetaxel in another randomized trial of second-line chemotherapy, which compared 100 or 75 mg/m^2 of docetaxel against a control regimen of vinorelbine or ifosfamide [21]. The docetaxel dose of 60 mg/m^2 might be optimal when it is combined with a standard dose of cisplatin. Additional study is warranted regarding this dose issue.

In summary, this randomized phase III trial demonstrates that DC is superior, in terms of response rate and survival, to VdsC in the treatment of previously untreated patients with stage IV NSCLC. A doubling in the 2-year survival rate is reported for DC compared with the classic standard regimen. Given the results of this trial, DC should be considered as a standard regimen for the first-line treatment of stage IV NSCLC, and it is suggested that the classic combination regimen should no longer be regarded as a suitable control arm in future randomized studies of patients with stage IV NSCLC.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Performed contract work within the last 2 years: Kaoru Kubota, Aventis Pharma Ltd; Koshiro Watanabe, Aventis Pharma Ltd; Hideo Kunitoh, Aventis Pharma Ltd; Kazumasa Noda, Aventis Pharma Ltd; Yukito Ichinose, Aventis Pharma Ltd; Nobuyuki Katakami, Aventis Pharma Ltd; Takahiko Sugiura, Aventis Pharma Ltd; Masaaki Kawahara, Aventis Pharma Ltd; Akira Yokoyama, Aventis Pharma Ltd; Soichiro Yokota, Aventis Pharma Ltd; Shuichi Yoneda, Aventis Pharma Ltd; Kaoru Matsui, Aventis Pharma Ltd; Shinzo Kudo, Aventis Pharma Ltd; Masahiko Shibuya, Aventis Pharma Ltd; Takeshi Isobe, Aventis Pharma Ltd; Yoshihiko Segawa, Aventis Pharma Ltd; Yutaka Nishiwaki, Aventis Pharma Ltd; Yasuo Ohashi, Aventis Pharma Ltd; Hisanobu Niitani, Aventis Pharma Ltd.

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Efficacy and Tolerability of Cancer Pain Management with Controlled-release Oxycodone Tablets in Opioid-naïve Cancer Pain Patients, Starting with 5 mg Tablets

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Background: We conducted an open-label, dose titration study to assess the efficacy and tolerability of controlled-release oxycodone in the therapy of cancer pain management, starting with a newly developed 5 mg tablet every 12 h.
Methods: Twenty-two Japanese cancer patients with pain who had not been taking opioid analgesics over the previous 2 weeks were enrolled. The length of time and the dose needed to attain stable and adequate pain control were evaluated in addition to the assessment of analgesic efficacy and safety during the study period.
Results: Eighteen patients in the efficacy population (18 out of 20, 90%) attained stable, adequate pain control. Two-thirds of the patients attained stable, adequate pain control without any dose titration. The mean length of time was 1.2 days. In these patients, the pain was significantly reduced in intensity, even at 1 h after the initial dose intake. Fifteen patients (68%) reported at least one side effect, but only one patient had to withdraw from the study because of a side effect.
Conclusion: The results suggest that controlled-release oxycodone tablets offered stable and adequate pain control within a short period of time in most Japanese cancer patients who have not been taking opioid analgesics, and could be effectively titrated against pain from a starting dose of 5 mg every 12 h. This indicates that a lower strength controlled-release oxycodone formulation may make it possible to start and titrate the dose more appropriately and carefully in patients who are sensitive to opioid analgesics.

Key words: oxycodone – 5 mg controlled-release tablets – titration – analgesia – cancer pain

INTRODUCTION

Oxycodone is a semi-synthetic opioid analgesic drug that has been in clinical use for >80 years (1). It effectively relieves both non-cancer and cancer pain in patients (2–4), and has been widely acknowledged as one of the invaluable alternatives to morphine, the parent drug of strong opioid analgesics (5,6).

The strengths of controlled-release (CR) oxycodone tablets legalized in Japan in April 2003 are 5, 10, 20 and 40 mg tablets. Since 1997, however, they have been widely available in the USA and Europe. We anticipated that a starting dose of lower than 10 mg would provide effective analgesia in cancer

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patients with moderate pain who had not previously been exposed to opioid analgesics, based on the dose ratio between morphine and oxycodone calculated in previous studies (7–10), which suggested that 5–7.5 mg of CR oxycodone would provide adequate analgesic effects comparable with those of 10 mg CR morphine tablets.

It should also be considered that a lower starting dose may be better tolerated in Japanese cancer patients with moderate pain, because the average body weight of Japanese individuals is much lower than that of Western individuals. Therefore, the starting dose of 10 mg may possibly lead to an overdose for some Japanese patients who have not been exposed to opioid analgesics previously. In addition, a lower starting dose should also be recommended for patients with renal and/or hepatic impairment in comparison with those with normal functions (11). These are the reasons why the 5 mg CR oxycodone tablets were developed to control slight to moderate pain that was not relieved with non-opioid analgesics. The tablet was also expected to be useful for cancer patients for whom a lower starting dose should be considered or a sensitive dose titration should be performed during the opioid treatment.

This was an open-label, 7 day dose titration study in cancer patients with pain who had not been taking opioid analgesics over the previous 2 weeks. The aim of this study was to determine the length of time and the dose needed for attaining stable and adequate pain control, and to evaluate the efficacy and safety of CR oxycodone tablets, with a starting dose of 5 mg every 12 h.

SUBJECTS AND METHODS

PATIENTS

This study was conducted over a 3 month period in adult in-patients with cancer pain recruited from 11 centers (13 divisions) in Japan. They were receiving non-opioid analgesics to manage their pain, but with little effect. The patients eligible for the study had to be cooperative, able to take oral medication and able to keep a pain diary. The patients enrolled scored their pain intensity as slight to severe pain on a 4-point categorical (CAT) scale (where 0 = no pain, 1 = slight pain, 2 = moderate pain and 3 = severe pain). They had been treated with non-opioid analgesics until entering the study, e.g. paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), but they had not taken any opioid analgesics over at least the previous 2 weeks. The values of their clinical laboratory tests for liver function (glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and total bilirubin) and kidney function (serum creatinine) should not exceed the upper limit of the in-house normal reference range by more than five and six times, respectively. Patients were excluded if they had a history of hypersensitivity to opioid analgesics or if the use of oxycodone or morphine was contraindicated for any reasons. Also excluded were patients who had undergone surgery or palliative radiotherapy for pain over the previous 2 weeks, or who were scheduled to undergo such treatments during the study period.

This study was designed mainly to assess pharmacokinetic profiles of CR oxycodone 5 mg tablet in a single dose as well as to evaluate the safety and efficacy of the CR oxycodone during the titration. For that purpose, 20 cases were considered necessary for the pharmacokinetic analysis and, therefore, we set the target number at 25 cases with the premise that there might be some cases to be excluded from the analysis set. However, infact, we decided to discontinue the study when 22 patients were accumulated, because we judged the number of patients to be sufficient to conduct the pharmacokinetic analysis. The relationship between pharmacokinetics of oxycodone and pain intensity after the first dose will be published separately (in preparation).

All patients gave written informed consent before being enrolled in the study. The institutional review board at each center approved the protocol before the study was initiated. The study was carried out in accordance with the guideline of Good Clinical Practice (GCP) and the ethical principles originating from the Declaration of Helsinki.

TREATMENTS

This was an open-label, dose titration study starting with a 5 mg CR oxycodone tablet given every 12 h. The initial dose was 5 mg and the dose could be titrated against the intensity of pain. If the patient reported their pain intensity as 'moderate' or 'severe' on the CAT scale, the dose could be titrated with the use of 5 and 20 mg CR oxycodone tablets every 24 h. Conversely, the doses could be reduced if the patient experienced intolerable adverse events. Dose titration against the intensity of pain was continued until a stable and adequate pain control with minimal adverse effect was obtained. We considered that adequate pain control was attained when the following conditions were fulfilled: pain-free period lasted at least 48 h; the dose every 12 h was unchanged; no supplemental analgesic dose was taken; the dosing regimen for any non-opioids or adjuvants was unchanged; the patients rated their pain intensity as 'no' or 'slight' on the CAT scale; and any adverse events were tolerable.

Throughout the study, patients were allowed to take immediate release oral morphine preparations as rescue medication whenever breakthrough pain or incident pain occurred. If patients took the rescue medication, an equivalent amount of oxycodone was added to their total daily dose of CR oxycodone tablets. The maximum daily dose of oxycodone (i.e. CR oxycodone tablets plus any rescue dose) permitted in this study was 240 mg.

Patients were not allowed to take any other opioid analgesic during the study. They were allowed to take non-opioid analgesics and adjuvant medications for their specific needs if these drugs had been given before study entry. The dose and route of administration of these drugs had to remain the same throughout the study course as they had been taking until study entry. The use of anti-side effect agents was recommended during the

study. In particular, anti-emetics and laxative agents were commonly used from study entry.

Pain Intensity

Each day, the patients themselves assessed their pain intensity over the previous 24 h. They were also requested to assess their pain intensity at 0 h (i.e. immediately before taking their initial dose of study medication), and at 1, 3, 5, 8 and 12 h after the initial dose intake. At the same points, blood samples were collected concomitantly and assayed for plasma oxycodone and noroxycodoen. They rated their pain intensity on the CAT scale described above, and on a 100 mm visual analogue scale (VAS), where 0 mm = a painless state and 100 mm = worst possible pain. Patients also recorded the number of hours that they were in pain each day and also the number of hours of sleep they had each day.

Evaluation of Pain Control and Length of Time to Attain Stable and Adequate Pain Control

The investigator at each center assessed whether the patient was under stable and adequate pain control in accordance with the criteria described above. The first assessment by the investigator was made 48 h after the initial intake of the study medication. Subsequent assessment was conducted each morning until the patient had attained a stable and adequate pain control.

When the patient attained a stable and adequate pain control within the first 48 h without any dose titration, the time to stable and adequate pain control was recorded as 0 day.

Acceptability of Therapy

Acceptability of therapy was an index based on analgesic effect and side effect of the study medication assessed by patients. Each day, the patients themselves assessed the acceptability of the therapy to them over the previous 24 h and recorded this in a diary. They rated the acceptability of therapy on the 5-point acceptability CAT scale (1 = very poor, 2 = poor, 3 = fair, 4 = good, 5 = excellent). The overall assessment was done in accordance with pain intensity and the occurrence of any adverse events.

Safety Assessments

Safety was evaluated based on the frequency and severity of adverse events, the data for which were obtained by questioning and/or examining the patients and by reviewing the patient's pain diaries and also the results of clinical laboratory tests at study entry and completion of, or withdrawal from, the study. The severity (slight, mild or severe) and seriousness (serious and non-serious) of adverse events was assessed by the investigators.

Statistical Analyses

The percentage of patients who gave a rating of 'good' or 'excellent' for acceptability of therapy were analyzed using the Clopper–Pearson method with a 95% confidence interval (CI).

Changes in the percentage of patients whose pain intensity was 'slight' and 'no' pain were assessed using the McNemar method. Changes in pain intensity (CAT scale and VAS scores) were assessed using the Wilcoxon signed rank test. The following parameters were analysed using the paired *t*-test: number of painful hours per day, number of hours sleep and acceptability of therapy ratings. The percentage of patients attaining stable and adequate pain control and the associated 95% CIs were estimated using the Kaplan–Meier method and Greenwood's method, respectively.

RESULTS

Patient Population

Of the twenty-two cancer patients enrolled in the study, 20 completed the 7 day study period. The efficacy population included 20 patients who were enrolled and did not infringe any of the inclusion or exclusion criteria. Two patients were excluded from the efficacy population because of infringement of the inclusion criteria: one patient had received a fentanyl injection (0.1 mg/day) for pain relief during biopsy 4 days before study entry; and the other patient had not been treated with any analgesic agents before the study. The safety population included all of the 22 patients who were enrolled and had received at least one dose of the study medication.

The mean age and mean body weight of all of the 22 patients were 69.1 years (range 49–80) and 54.5 kg (range 38.0–82.0), respectively. Nineteen patients (86.3%) were male. The most common diagnosis was lung cancer (25.0%), followed by stomach and esophageal cancer. The most common sites of pain were the chest and abdomen.

Two patients withdrew from the study. One withdrew because of the complication of serious pneumonia, which was not considered to be related to the study medication. The other withdrew because of somnolence, which was considered to be related to the study medication. This patient had attained stable and adequate pain control before the withdrawal.

Time Course of Pain Intensity After the Initial Dose

Table 1 shows patients' pain intensity scores (CAT scale) up to 12 h after the initial dose intake of the study medication (one 5 mg tablet). The patients' pain intensity scores decreased significantly by 1 h after the intake and the decreases continued up to 12 h after.

A similar time course of pain intensity was observed when assessed using the VAS. No patient needed supplemental medication until the next dose was given.

Requirements for Titration

Eighteen of the 20 patients (90%) attained stable and adequate pain control during the 7 day study period. Table 2 shows the

Table 1. Changes in pain intensity up to 12 h after the initial dose

Time points (time after initial dose, h)	CAT pain intensity score*		VAS pain intensity score	
	Mean ± SD	*P*-value**	Mean ± SD	*P*-value**
0	1.7 ± 0.8	–	44.0 ± 24.8	–
1	1.3 ± 0.9	0.0078	33.0 ± 31.2	0.0022
3	1.2 ± 0.9	0.0078	32.1 ± 31.8	0.0100
5	1.0 ± 0.9	0.0020	27.1 ± 29.9	0.0016
8	1.2 ± 0.9	0.0156	31.8 ± 30.8	0.0314
12	1.3 ± 0.9	0.0469	32.1 ± 30.1	0.0285

$n = 20$ at all time points.
*CAT pain score: 0 = no pain; 1 = slight pain; 2 = moderate pain; 3 = severe pain.
**P-value for change from 0 h after the initial dose.

Table 2. Mean length of time to stable, adequate pain control and mean dose needed for stable, adequate pain control*

	Mean ± SD	Minimum	Median	Maximum
Length of time to adequate, stable pain control (days)	1.2 ± 1.9	0	0	5
Dose needed for adequate, stable pain control (mg/day)	16.7 ± 10.8	10.0	10.0	40.0

*Patients attained stable, adequate pain control, $n = 18$.

mean (±SD), minimum, median and maximum length of time and the dose needed to obtain stable and adequate pain control. Mean (±SD) and median length of the time to stable, adequate pain control were 1.2 ± 1.9 and 0 days, respectively. Mean (±SD) and median doses needed for stable and adequate pain control were 16.7 ± 10.8 and 10 mg/day, respectively. The dose ranged from 5 to 20 mg every 12 h. Two patients were unable to attain stable adequate pain control during the study period: one withdrew because of an adverse event (pneumonia), and the other did not want to increase the study medication because of adverse events (sleepiness, itching, sweating and dry mouth). The estimated rate of achievement of stable and adequate pain control at the end of the study was 93.8% (95% CI 82.1–100.0).

Table 3 shows the number and percentage of patients who attained stable and adequate pain control at each dose level. Twelve (68%) of the 18 patients attained it at the dose of 5 mg every 12 h (10 mg/day). All of these patients required no dose titration and attained pain relief that met the criteria for stable and adequate pain control. They attained it within the first 48 h after study entry (length of time to stable and adequate pain control is 0 days).

Change in Pain Intensity During the Study

At study entry, 13 patients (65%) reported their pain intensity to be 'moderate' to 'severe' and seven patients (35%) reported it to be 'slight'. Table 4 shows the patient mean (±SD) CAT scores at study entry reported by the patients, 24 h after their initial dose intake of the study medication, and at the end of the study. The decrease in patients' pain intensity between study entry and 24 h after their first dose of study medication, and that between study entry and at the end of study were both statistically significant. Similar decreases were also observed and found to be statistically significant in making an assessment of patients' pain intensity with the use of the VAS.

Table 3. Number and percentage of patients attaining stable, adequate pain control at each daily dose

Daily dose (mg)	No. (%) of patients attaining stable, adequate pain control
10	12* (68)
20	2 (11)
30	2 (11)
40	2 (11)

*All 12 patients attained stable, adequate pain control on the first day.

The percentage of patients whose pain intensity was 'slight' and 'no' increased during the study. At the study entry, this rate was 35.0% (95% CI 15.4–59.2). The corresponding values at 24 h after the initial dose intake and at the end of the study were 70% (95% CI 45.7–88.1) and 87.5% (95% CI 61.7–98.4), respectively. The increase in the percentage of the patients whose pain was 'slight' and 'no' was statistically significant between study entry and 24 h after their initial dose intake, and between study entry and the end of the study ($P = 0.0082$).

As rescue medication, more than one dose of immediate-release morphine was used in four patients (20%) during the 7 day study period. The mean of the rescue doses per day was 1.3 ± 0.5. Eighty percent of the patients required no rescue medication.

The number of hours each day that the patients were in pain decreased during the study period. At study entry, the median (range) number of painful hours per day was 12.0 h (1.0–24.0). At 24 h after the initial dose intake, it had decreased to 3.5 h (0.1–24.0), and this decrease was statistically significant ($P = 0.0155$). At the end of study, the corresponding value was 1.0 h (0.0–18.0), and this decrease from baseline (at study entry) was also statistically significant ($P = 0.0022$).

There was no change in the number of hours of sleep patients had each night during the study period. At study entry, the mean (SD) number of hours of sleep was 7.4 h (2.1). The corresponding values at 24 h after the first dose intake of the study medication and at the end of study were 7.7 h (2.3) and 7.3 h (1.9), respectively.

Acceptability of Therapy

Figure 1 shows the acceptability of the therapy to patients at study entry and at the end of the study. At study entry, the number of patients who rated the acceptability of the therapy as 'poor' or 'very poor' was 11 (55%); at the end of the study, this decreased to 1 (5%). The change in acceptability of therapy to patients measured on a 5-point acceptability CAT scale

Table 4. Pain intensity at study entry, at 24 h after the first dose and at the end of study

	VAS pain intensity score		CAT pain intensity score		Percentage of 'slight' or 'none' patients (%)	*P*-value**
	Mean ± SD	*P*-value**	Mean ± SD	*P*-value**		
At study entry	47.7 ± 26.4	–	1.8 ± 0.7	–	35.0	–
24 h after first dose	28.8 ± 22.3	0.0053	1.2 ± 0.8	0.0098	70.0	0.0588
At the end of the study*	15.7 ± 16.6	0.0025	0.9 ± 0.6	0.0010	87.5	0.0082

$n = 20$ at study entry and 24 h after first dose.
*$n = 16$: at the end of the study (i.e. at 12 h after the final dose), four patients were excluded from the analysis set as "non-evaluated" cases.
**P-value for change from study entry.

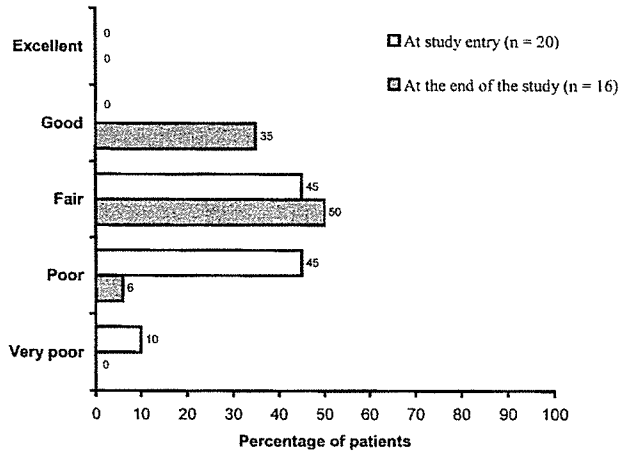

Figure 1. Patients' ratings of the acceptability of therapy at study entry and at the end of the study.

between study entry and at the end of study was statistically significant ($P = 0.0024$).

The percentage of patients whose rating of acceptability on a 5-point acceptability CAT scale was 'good' or 'excellent' was 0% (95% CI 0–16.8) at study entry. However, at the end of study, it increased to 43.8% (95% CI 19.8–0.1).

Safety Evaluations

At least one adverse event, which was considered by investigators to be at least possibly related to study medication (side effect), was observed in 15 of 22 patients (68%; 95% CI 45–86), and 41 cases occurred in total. The common (>10%) side effects were as follows: sleepiness (11 patients, 50%), constipation (seven patients, 32%), nausea (five patients, 28%) and anorexia (four patients, 18%). Most of the reported side effects were slight to moderate in severity. Six cases of severe side effects were reported. Except for one patient who had to discontinue the study due to severe somnolence, all of the patients were able to continue the treatment with the study medication in spite of the side effects. It should be noted that no serious side effects were reported.

Only one patient withdrew from the study because of somnolence that might be related to the study medication. There was no other serious side effect.

Abnormal changes either in white blood cell count or blood creatinine were seen in two patients (9%). Abnormal changes in glutamic oxaloacetic transaminase, glutamaic pyruvic transaminase or positive urinary protein were seen in one patient. Changes in glutamic oxaloacetic transaminase and glutamaic pyruvic transaminase were considered to be clinically significant and considered to be related to the study medication.

Both of the clinical laboratory test values were 21 U before study entry and 51 U at the end of study. The investigator considered that it was impossible to deny the causal relationship between the study medication and the change in laboratory values, although many other drugs were used concomitantly with study medication and, therefore, the exact cause of this abnormal change in laboratory values could not be determined. These changes returned to normal after the medication was stopped.

The value of daily risk was calculated by the method of dividing the total number of incidents of seven common adverse events associated with the opioid, namely constipation, vomiting, nausea, sleepiness, dizziness, dry mouth and pruritus, by the total number of days on which the tablets were taken. The mean value of daily risk in the safety population was 0.19 (29 occurrences in 151 days). The mean value of daily risk in patients who attained stable and adequate pain control was 0.19 (23 occurrences in 125 days).

DISCUSSION

The World Health Organization three-step analgesic ladder has been widely used in cancer pain management (12). In many clinical settings, pharmacological treatment for mild, and sometimes moderate, cancer pain may often be initiated with non-opioid analgesic medication. It may progress to weak and then strong opioid medication in combination with non-opioid treatments as the pain increases in intensity. The only weak opioid analgesics available in Japan are codeine and hydrocodeine. Their analgesic effect is due to their conversion to morphine (13) and they have a ceiling effect. This makes treatment with weak opioid analgesics inappropriate for severe cancer pain management. Hence, the strong opioids are prescribed occasionally when treatment with non-opioid analgesics is ineffective, skipping a trial of weak opioid analgesics in clinical practice. Sometimes, small doses of strong opioids, such as morphine and oxycodone, are used

instead of weaker ones in step 2 for patients who are resistant to or no longer responding to NSAIDs. On the other hand, fixed-dose combination tablets of oxycodone and acetaminophen have been used effectively as weak opioid analgesics to control mainly non-opioid-irresponsive cancer pain in some countries including the USA. We thus conducted an open-label, dose titration study in Japanese cancer patients with pain who had not been taking opioid analgesics, with the starting dose of a 5 mg CR oxycodone tablet every 12 h.

Prior to this study, another study of similar design was conducted in Japanese cancer patients with pain (in preparation). Ninety-two opioid-naïve patients were enrolled in that study and the starting dose was 10 mg every 12 h (twice as high as this study). Twenty-four of 92 patients (26.1%) had to withdraw from the study within 10 days and half of them had to withdraw from the study within 2 days after the study started because of the adverse events (nausea, vomitting, sleepiness, dizziness, etc.) that are commonly associated with opioid analgesics, and most of these withdrawals (21 out of 24) occurred at the starting dose. However, 19 of the 24 patients (79.2%) reported that their pain was less than or equal to 'slight pain' on the pain score (CAT). It should be admitted that the study drug was administered without enough provisions against the side effects. However, a high incidence of sleepiness (five out of 24) and dizziness (three out of 24) associated with the study drug, which ultimately led to discontinuation of the study, suggested that the starting dose of a 10 mg CR oxycodone tablet might be too high for some Japanese cancer patients with pain who had not been taking opioid analgesics. This was possibly because the average weight of Japanese patients is less than that of Western patients.

Furthermore, since oxycodone elimination is delayed by renal (14) or hepatic impairment (15), lower dose CR oxycodone should be considered in determining the starting dose for those patients sensitive to opioids with renal or hepatic impairment. These are the main reasons for development of the 5 mg CR oxycodone tablet in Japan in addition to introduction of 10, 20 and 40 mg CR oxycodone tablets. In the present study, we tried to evaluate the clinical efficacy and safety of CR oxycodone tablets with a starting dose of 5 mg every 12 h in those Japanese cancer patients with non-opioid-irresponsive pain.

Patients who still had a pain unsatisfactorily treated with non-opioid analgesics were enrolled in this study. The aim of this inclusion criterion is to include potential target patients for the 5 mg tablet. Although seven patients (35%) reported baseline pain intensity to be 'slight' at study entry on a 4-point CAT scale, we considered that these patients needed opioid therapy. This was eventually shown by the fact that none of them rated their acceptability of therapy at study entry as 'satisfactory' or 'very satisfactory' on a 5-point acceptability CAT scale. However, at the end of the study, three patients showed satisfaction with the lower dose oxycodone treatment and, moreover, there was no patient who rated their acceptability of therapy as 'poor' or 'very poor'. These results suggest that opioid therapy was indeed needed for the patients with slight pain at study entry in this study.

The 5 mg CR oxycodone tablet (a newly developed formulation) gave significant pain relief 1 h after the first dose, and the subsequent pain scores were kept significantly lower than the pre-dose scores during the following 12 h period. In addition, score for pain intensity was significantly reduced over the 24 h after the first dose intake of 5 mg of study medication as compared with that at study entry. These data indicate that the 5 mg tablet is effective for controlling cancer pain and can be administered quite safely as the starting dose for Japanese cancer patients who have not previously been taking any opioid analgesics.

In this study, 18 (90%) of the 20 patients attained stable and adequate pain control throughout the study period. Two-thirds of them did so on a dose of 5 mg every 12 h without further titration within the initial 48 h (at 0 day). The mean length of time to achieve stable and adequate pain control was 1.2 days. This result was consistent with the findings in two previous studies with CR oxycodone which showed that the mean length of time to stable and adequate pain control was 1.6–2 days (8,16). Although it is common practice to start opioid therapy with an immediate-release formulation and titrate the dose against pain intensity, Salzman and colleagues reported that CR oxycodone was also as readily titrated as an immediate-release formulation (16). Our results support their findings. Moreover, both the patients' rating of their acceptability of therapy on a 5-point acceptability CAT and the overall improvement assessment by the investigator were significantly improved at the end of this study. These results suggest that the use of 5 mg CR oxycodone tablets, if necessary with titration, is acceptable for cancer patients who had not been taking opioid analgesics and is effective for them to achieve stable and adequate pain control in a short period of time.

The 5 mg CR oxycodone tablet was developed to offer a lower starting dose for patients who might experience intolerable adverse events with a starting dose of 10 mg every 12 h. Although a high percentage of patients reported adverse events during this study, most of them were reported to be slight to moderate in severity and only one patient withdrew because of an adverse event (somnolence). Sleepiness, constipation and nausea were the three most common adverse events, all of which are widely known side effects of most opioid analgesics. Another adverse event commonly observed in this study was anorexia, which is commonly reported by cancer patients with pain and can be exacerbated by opioid administration (17).

In conclusion, CR oxycodone tablets offered stable and adequate pain control within a short period of time in most Japanese cancer patients who have not been taking opioid analgesics, and could be effectively titrated against pain from a starting dose of 5 mg every 12 h. Most of the side effects were tolerable. This indicates that a lower strength CR oxycodone formulation may make it possible to start and titrate the dose more appropriately and carefully in patients who are sensitive to opioid analgesics, including Japanese cancer patients who have a relatively lighter body weight, or patients with renal and/or hepatic impairment.

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Genome-wide cDNA microarray screening of genes related to the benefits of paclitaxel and irinotecan chemotherapy in patients with advanced non-small cell lung cancer

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Previous studies have demonstrated that not only the benefits but also the toxicities of chemotherapy can be predicted by cDNA microarray analysis of tumor specimens obtained before chemotherapy against non-small cell lung cancer (NSCLC). We conducted a study of cDNA microarray analysis to determine whether the gene expression in peripheral blood taken from patients prior to chemotherapy were correlated with the outcome of chemotherapy with paclitaxel (Pac) and irinotecan (CPT) against advanced NSCLC . Thirty-one patients with stage IIIB or IV NSCLC were treated with CPT at 60 mg/m^2 and Pac at 160 mg/m^2 every 2 weeks. Seventeen of 31 patients achieved PR and the overall RR was 54.8%. The median survival time was 426 days and the 1-year survival rate was 58.1%. The expression levels of 1176 genes were analyzed in 31 patients with the AtlasTM Human Cancer 1.2 Array. Stepwise multivariate analysis revealed that the genes encoding protein phosphatase, IL-1α and IgA were independent predictive factors for chemosensitivity. Stepwise regression analysis revealed that the thyrotropin-releasing hormone receptor and alkylation repair genes were independent prognostic factors. In conclusion, the expression of certain genes was able to predict the benefits of this Pac and CPT chemotherapy regimen.

Key words: microarray, paclitaxel, irinotecan, lung-cancer, gene

INTRODUCTION

Current chemotherapy regimens for metastatic non-small cell lung cancer (NSCLC) are not particularly effective, and the disease cannot be cured even with the most effective chemotherapy. Responders to chemotherapy may have a better prognosis than non-responders (1) and chemosensitivity is an important factor in deciding which patients should receive chemotherapy in such non-curative NSCLC. Previous study has demonstrated that not only the benefits but also the toxicities of chemotherapy can be predicted by cDNA microarray analysis of tumor specimens obtained before chemotherapy (2). The results suggest that the intrinsic genetic characteristics of individual patients will reflect the outcomes of chemotherapy and lead to the hypothesis that genetic analysis of non-malignant cells can also be used to predict the benefits and toxicities of chemotherapy.

Our previous phase I study of a paclitaxel (Pac) and irinotecan (CPT) combination led to a recommendation of Pac 160 mg/m^2 and CPT 60 mg/m^2 every 2 weeks for further study (3). This study also demonstrated an objective response rate of 58.3%, and a 1-year survival rate of 54.2%. Accordingly, we examined the correlations between gene expression in peripheral blood, which is easily available, and the benefits of the combination chemotherapy with Pac and CPT to display high activity against NSCLC.

Table 1. Patient characteristics

No. of patients		
Total		31
Age, years	Median	61
	Range	43 – 69
Gender	Male	20
	Female	11
Performance status (ECOG)	0	9
	1	22
Clinical stage	IIIB	5
	IV	26
Histology	Adenocarcinoma	24
	Others	7

PATIENTS AND METHODS

The Institutional Review Board of Kanagawa Cancer Center reviewed and approved this study prior to commencement.

Patients. Patients with histologically or cytologically confirmed NSCLC were registered. Eligibility criteria were: clinical stage IIIB or IV, age <70 years, Eastern Cooperative Oncology Group PS score ≤1. Patients who had received chemotherapy or radiotherapy were excluded from this study. Written informed consent was obtained from every patient.

Chemotherapy. All patients without disease progression were treated every 2 weeks for a total of four courses of chemotherapy. CPT was administered at a dose of 60 mg/m^2 on day 1. Pac was administered at a dose of 160 mg/m^2 on day 1. Premedication consisting of 20 mg dexamethasone and 50 mg ranitidine was infused. A 50 mg oral dose of diphenhydramine was also administered. Prophylactic G-CSF, 50 μg/m^2/day or 2 μg/kg/day, was administered subcutaneously on days 6 to 10. Patients were given a 5-HT$_3$ antagonist intravenously. Tumor response was evaluated according to RECIST criteria (4).

Blood samples, purification of RNA and cDNA microarray. Genomic DNA was obtained from peripheral blood mononuclear cells (PMNC) isolated from 10 ml of peripheral blood taken from patients prior to chemotherapy. The total RNA of each sample was isolated and treated with DNase I to avoid contamination by genomic DNA by using silica membrane affinity chromatography and a total RNA isolation kit (Macherey-Nagel GmbH & Co., KG, Germany). One hundred nanograms of the total RNA for each sample was reverse transcribed into cDNA. Each cDNA sample was subjected to microarray expression profiling with the BD Atlas™ Human Cancer 1.2 Array (Clontech) (2). Each labeled probe was then hybridized into a separate Atlas Array. The signal intensity for each spot, which corresponds to each gene examined, was determined with a STORM image analyzer (Amersham Bioscience, Picataway, NJ). The hybridization pattern and signal intensity were analyzed to determine changes in gene expression levels by using AtlasImage™ 2.01 software (Clontech Laboratory Inc., Japan).

Statistical methods. The association between gene expression and tumor regression during chemotherapy was tested with the Pearson correlation coefficient. To determine whether gene expression profiles were associated with differences in survival, Kaplan-Meier survival plots and log-rank tests were used. The influence of expression of each gene on chemotherapy outcomes was examined by stepwise multivariate regression analysis or cox proportional hazards model analysis. $P < 0.05$ was considered significant.

RESULTS

Between May 2002 and July 2004, 31 patients were registered in the study (Table 1). Twenty-seven patients received 4 to 6 cycles of chemotherapy, except for 4 patients who discontinued treatment in the first or second cycles because of disease progression in 3 patients and grade 2 pneumonitis in 1 patient. Seventeen of 31 patients achieved PR, 10 NC and 4 PD, and the overall RR was 54.8% in this study. The median survival time was 426 days and the 1-year survival rate was 58.1%.

The expression levels of 1176 genes in the peripheral blood cells of 31 patients were analyzed by cDNA microarray screening. Four housekeeping genes that were expressed in all 31 samples were used as controls for gene expression: ubiquitin, liver glyceraldehyde 3-phosphate dehydrogenase, 23-kDa highly basic protein, 60S ribosomal protein L13A and 40S ribosomal protein S9.

Stepwise multivariate analysis revealed that protein phosphatase with EF-hands-2 long form, IL-1α and IgA 1 heavy chain constant region + IgA2 heavy chain constant region were independent predictive factors for chemosensitivity ($p < 0.001$, Table 2). Of these genes, expression of protein phosphatase and IL-1α was positively, and expression of IgA was negatively, correlated with tumor regression rate. When we analyzed the relationship between gene expression levels and survival, the expressions of 10 genes were significantly correlated with survival times ($p < 0.01$). Stepwise regression analysis revealed that thyrotropin-releasing hormone receptor and alkylation repair genes were independent prognostic factors ($p < 0.01$, Table

Table 2. *Genes closely associated with sensitivity or survival in chmeotherapy.*

	Description	coefficient	P
Sensitivity	protein phosphatase with EF-hands-2 long form	-0.436	0.0134
	IL-1 alpha	-0.432	0.0145
	IgA 1 heavy chain constant region+ IgA 2 heavy chain constant region	0.463	0.008
Survival	thyrotropin-releasing hormone receptor	0.509	0.0029
	alkylation repair; alkB homologue	0.489	0.0046

Stepwise multivariate analysis for sensitivity and stepwise regression analysis for survival were used.

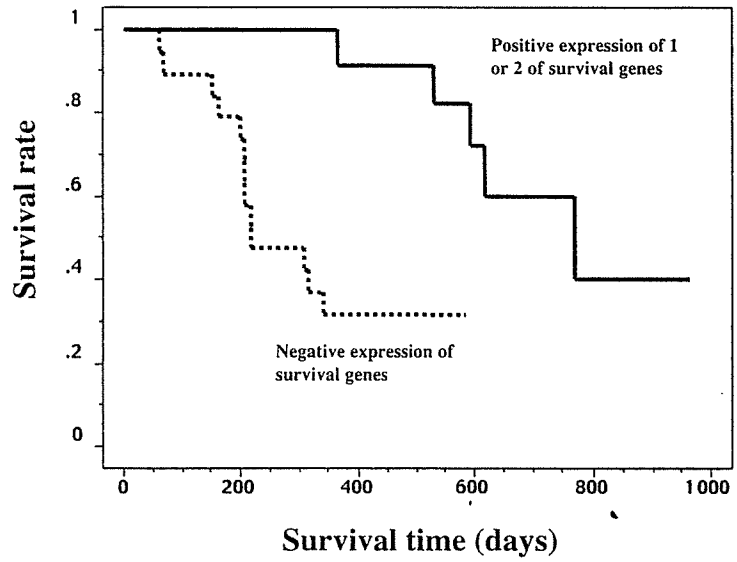

Figure 1. Survival curves constructed by the Kaplan-Meier method. The 12 of the 31 patients who showed positive expression of either the thyrotropin-releasing hormone receptor or alkylation repair genes had a significantly better chance of survival (log-rank, p = 0.0024; Wilcoxon, p = 0.0016)

2). The 12 of the 31 patients who showed positive expression of either thyrotropin-releasing hormone receptor or alkylation repair genes had a significantly better chance of survival (log-rank, p = 0.0024; Wilcoxon, p = 0.0016; Fig. 1). Cox proportional hazards model demonstrated that positive expression of these genes was only significantly dependent prognostic factor (p=0.0094, Table 3).

DISCUSSION

We previously reported that examination of tumor tissues revealed a number of genetic predictors not only of beneficial but also of toxic effects of cancer chemotherapy (2). The fact that genetic information from tumor cells can predict not only tumor susceptibility to chemotherapy but also toxicity suggests that certain genetic characteristics may be common to all somatic cells, irrespective of whether they are malignant or normal. To add support for this hypothesis, in this study we used peripheral blood cells as non-malignant normal cells for analysis of informative genetic factors that can predict the antitumor effects. Protein phosphatase, IL-1α and IgA were predictors of sensitivity to Pac and CPT combination chemotherapy. The adenoviral type 5 E1A protein has been shown to induce sensitization to apoptosis induced by different categories of anticancer drug. Up-regulation by E1A of the catalytic subunit of protein phosphatase 2A in human breast cancer cells was shown to enhance the activity of the phosphatase, which resulted in repression of Akt

Table 3. *Cox Proportional Hazards Model for Survival Analysis in paclitaxel and irinitecan treatment.*

		Hazard Ratio	95% CI	P
Gender	Female/Male	0.701	0.127-3.86	0.6833
Performance status	0/1	0.706	0.173-2.872	0.6264
Stage	IIIB/IV	0.247	0.030-2.024	0.1926
Hb		0.956	0.534-1.714	0.8803
Albumin		0.405	0.109-1.504	0.1770
LDH		1.002	0.997-1.006	0.4442
Survival gene	Negative/Positive	9.102	1.720-48.180	0.0094

activation in E1A-expressing cells (5). This up-regulation of protein phosphatase 2A might represent a novel mechanism for E1A-mediated sensitization to anticancer drug-induced apoptosis. IL-1α is a cytokine with many activities central to immune function and hematopoesis. This cytokine dramatically increases the sensitivity of osteosarcoma cells to etoposide when the two agents are used simultaneously (6). Thyrotropin-releasing hormone (TRH) receptor and alkylation repair genes were identified as independent prognostic factors. TRH plays a key role in the regulation of the thyroid axis. A number of changes in hormonal secretion patterns have been found in subjects with neoplastic disease. When mean nocturnal levels were compared, cortisol, TRH and growth factor levels were higher in patients with lung cancer than in normal controls (7). TRH and its receptor are also expressed in non-hypothalamic cells such as pancreatic cells, suggesting that TRH might play a biological role in an autocrine fashion (8). It is possible that a TRH-related autocrine system in normal cells may overcome the cachexia induced by lung cancer.

The development of cancer involves the concurrent disruption of regulation of expression of multiple genes. Therefore, DNA repair systems play an important role in tumor growth and patient survival. The acquisition of methylation of the DNA mismatch repair gene hMLH1 in plasma DNA after chemotherapy predicts poor survival for ovarian cancer patients (9), suggesting that depression of the repair system increases tumor growth and decreases patient survival time. It therefore appears reasonable that the present study showed that increased expression of alkylation repair genes is correlated with good survival.

We need to undertake prospective evaluations to determine whether the genes revealed in this study are truly important and potentially useful for predicting the beneficial of chemotherapy. Accumulation of such data could eventually allow chemotherapy to become "personalized", allowing the use of anticancer drugs that are effective in individual patients.

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Genomewide cDNA Microarray Screening of Genes Related to Benefits and Toxicities of Platinum-Based Chemotherapy in Patients With Advanced Lung Cancer

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Abstract: The authors conducted a study using cDNA microarray analysis to determine whether expression levels of genes in tumors were correlated with the outcome of chemotherapy. Forty-seven patients were studied, and all except 3 received platinum-based chemotherapy. The expression levels of 1176 genes in transbronchial biopsy specimens of tumors that were obtained before chemotherapy were analyzed using the Atlas Human Cancer 1.2 Array. Multivariate regression analysis revealed that 3 genes were each independent factors related to tumor resistance to chemotherapy and patient survival ($P < 0.01$). Among various chemotherapy-related toxicities, 1, 3, 3, 1, and 1 genes were also revealed to be independent factors that were correlated with neutropenia, anemia, diarrhea, infection, and increased serum creatinine respectively ($P < 0.01$). It is concluded that not only the benefits but also the toxicities of chemotherapy can be predicted by cDNA microarray using tumor specimens obtained before chemotherapy.

Key Words: microarray, gene, lung, cancer

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Lung cancer is a disseminated disease, and most affected patients are candidates for chemotherapy. Although responders to chemotherapy may have a better prognosis than nonresponders,[1] even the most effective chemotherapy cannot always reduce the tumor volume of lung cancer. The properties of cancer cells are determined by complicated interactions among all the gene products they express, and it is certain that many proteins—including enzymes involved in apoptosis, DNA repair, and the metabolism and detoxification of drugs—have individual responses. The cDNA microarray method is now widely used to analyze the expression of thousands of genes simultaneously in cancer tissues, and its development has facilitated the analysis of genomewide expression profiles. Using the cDNA microarray technique on tumor tissues obtained before chemotherapy, we previously identified 3 independent genes, each of which is correlated with chemoresistance and patient survival.[2,3] However, another important aspect of chemotherapy apart from tumor susceptibility and patient survival is the extent of adverse effects. Some cancer patients suffer severe adverse effects of chemotherapy regardless of whether their tumors are chemosensitive. Such patients are unable to receive repeat courses of chemotherapy, even if they have shown a tumor response. Accordingly, it is important to be able to predict not only patients who are likely to respond to chemotherapy, but also those who will probably experience severe treatment-related toxicities.

The current study analyzed the correlation between the expressions of various genes in tumor specimens and chemotherapy-related toxicities, and compared the genes related with the beneficial and toxic effects of chemotherapy.

PATIENTS AND METHODS

Patients

This study was approved by the institutional review board of Kanagawa Cancer Center. Patients with histologically proved lung cancer treated with chemotherapy were entered into the study. All were eligible for treatment. They had an expected survival of at least 6 weeks, measurable lesions, Eastern Cooperative Oncology Group performance status score ≤3 points, a white blood count of ≥4000 cells/μL, hemoglobin ≥10 g/dL, platelet count ≥100,000 platelets/μL, total serum bilirubin less than 2 mg/dL, aspar-

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