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 ($P = .20$).

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.

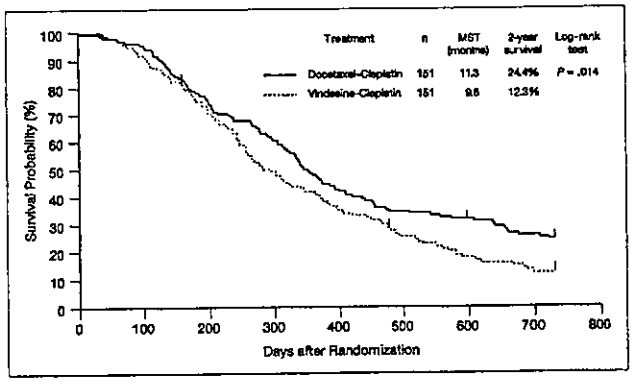

Fig 2. Kaplan-Meier survival estimates for patients treated with docetaxel plus cisplatin and patients treated with vindesine plus cisplatin. MST, median survival time.

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.

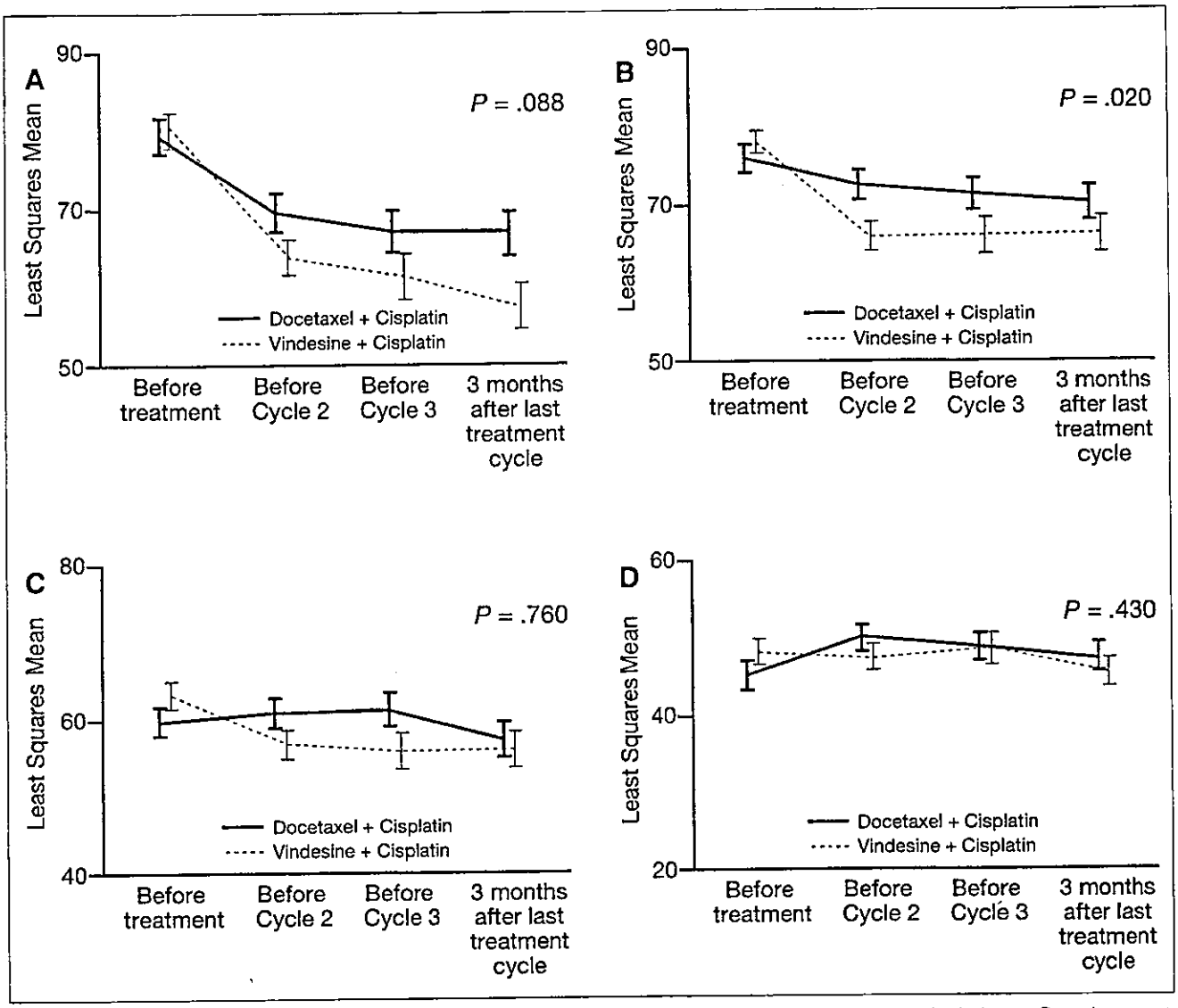

Fig 3. Quality-of-life assessments across four domains of the Quality of Life Questionnaire for Cancer Patients Treated with Anticancer Drugs instrument, among patients treated with docetaxel plus cisplatin and vindesine plus cisplatin. (A) Functional; (B) physical; (C) mental; and (D) psychosocial.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

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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Original article

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A phase II study of cisplatin and docetaxel administered as three consecutive weekly infusions for advanced non-small-cell lung cancer in elderly patients

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Background: To evaluate the efficacy and safety of treatments for advanced non-small-cell lung cancer in elderly patients aged 75 years or older, we conducted a phase II study of cisplatin and docetaxel administered in three consecutive weekly infusions.

Patients and methods: The eligibility criteria for the study included the presence of chemotherapy-naive advanced non-small-cell lung cancer, age ≥75 years, Eastern Cooperative Oncology Group performance status of 0 or 1, a measurable lesion, adequate organ functions and signed informed consent. The chemotherapy regimen consisted of cisplatin (25 mg/m^2) and docetaxel (20 mg/m^2) on days 1, 8 and 15 every 4 weeks.

Results: Between February 2000 and March 2002, 34 elderly patients with non-small-cell lung cancer were enrolled in the study and 33 patients were treated. Two complete responses and 15 partial responses were obtained for an objective response rate of 52% in 33 treated patients. The median survival period was 15.8 months, and the 1-year survival rate was 64%. Toxicities were mild with no grade 4 toxicities. Only grade 3 leukopenia (6%), neutropenia (12%), anemia (3%), hyponatremia (3%) and nausea/vomiting (3%) were observed.

Conclusion: Cisplatin and docetaxel administered in three consecutive weekly infusions was safe and effective for the treatment of elderly patients with chemotherapy-naive non-small-cell lung cancer.

Key words: cisplatin, docetaxel, elderly patients, non-small-cell lung cancer, weekly administration

Introduction

Lung cancer is one of the most common carcinomas not only in Japan, but also in the United States and Europe. More than 55 000 patients die from lung cancer each year, and the mortality rate is still increasing in Japan [1, 2]. In particular, the number of elderly lung cancer patients is increasing in Japan [1, 2]. Surgery is the most effective curative treatment for early stage non-small-cell lung cancer (NSCLC); however, only 30% of patients with NSCLC receive a curative resection [3]. Cisplatin-based chemotherapy offers a survival benefit and symptom relief for patients with inoperable NSCLC [4]. However, we have demonstrated that classic standard cisplatin-based chemotherapy regimens such as cisplatin (80 mg/m^2) on day 1 with etoposide (100 mg/m^2) on days 1–3 or cisplatin (80 mg/m^2) on day 1 with vindesine (3 mg/m^2) on days 1 and 8 cause severe myelotoxicity in elderly NSCLC patients aged ≥75 years [5]. We used a very restricted eligibility criteria to select patients who could tolerate the cisplatin-based standard chemotherapy. Among 34 elderly patients, only 10 fitted the eligibility criteria. In spite of granulocyte colony-stimulating factor (G-CSF) support, nine of the 10 eligible patients experienced grade 4 neutropenia and six had infectious episodes [5]. Thus, we hypothesized that the recommended dose for elderly patients aged ≥75 years should be determined in a specific phase I study only for elderly patients.

Docetaxel has demonstrated antitumor activity in NSCLC patients with chemotherapy-naive lesions and tumor progression after receiving cisplatin-based regimens [6–10]. Docetaxel with cisplatin is one of the most promising chemotherapy regimens for NSCLC [11]. The commonly used dose and schedule of docetaxel is 60–100 mg/m^2 every 3 weeks; however, moderate to severe neutropenia is frequently observed [6–11]. Recent studies have shown that weekly administration of docetaxel produces a higher dose intensity and less myelotoxicity [12–14]. Thus, we conducted two independent phase I studies for elderly and non-elderly patients with NSCLC to determine the recommended dose for phase II studies and to evaluate the safety and efficacy of cisplatin and docetaxel administered as three consecutive weekly infusions in both non-elderly (≤74 years) and elderly (≥75 years) patients

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[15]. Different recommended doses of docetaxel were obtained for non-elderly and elderly patients [15]. The recommended doses were 25 mg/m^2 cisplatin and 35 mg/m^2 docetaxel on days 1, 8 and 15 for non-elderly patients, and 25 mg/m^2 cisplatin and 20 mg/m^2 docetaxel on days 1, 8 and 15 for elderly patients.

Two phase II studies of cisplatin and docetaxel administered as three consecutive weekly infusions for non-elderly and elderly patients were conducted. The results of the phase II study for non-elderly patients with NSCLC have been reported elsewhere; the objective tumor response was 30% [95% confidence interval (CI) 15% to 46%] and the median survival time was 12.8 months [16]. Here, we report the promising results of a phase II study for elderly patients with NSCLC.

Patients and methods

Patient selection

Patients with histologically and/or cytologically documented NSCLC were eligible for the study. Each patient was required to meet the following criteria: clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy), an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, age ≥75 years, no prior chemotherapy, measurable lesions, adequate hematological function [white blood cell count (WBC) 4000–12 000/mm^3; neutrophils ≥2000/mm^3; platelets ≥100 000/mm^3; hemaglobin ≥9.0 g/dl], adequate hepatic function (total bilirubin <1.1 mg/dl, aspartate aminotransferase and alanine aminotransferase <60 IU/l), and adequate renal function (creatinine ≤1.2 mg/dl, creatinine clearance ≥60 ml/min). Patients with active infection, severe heart disease, uncontrollable hypertension or diabetes mellitus, active concomitant malignancy and pleural and/or pericardial effusion requiring drainage were excluded. The study was approved by the Institutional Review Board at the National Cancer Center, Yokohama Municipal Citizen's Hospital and Niigata Cancer Center. Written informed consent was obtained from each patient.

Patient evaluation

The pretreatment evaluation consisted of complete blood cell count, differential count, routine chemistry measurements, a chest radiograph, a chest computed tomography (CT) scan, abdominal ultrasound or CT scan, whole-brain magnetic resonance imaging or CT scan, and an isotope bone scan. Complete blood cell count, differential, count and routine chemistry measurements were carried out at least twice a week during the first course of chemotherapy.

Treatment schedule

All patients were admitted to hospital during the first course of chemotherapy. Chemotherapy consisted of cisplatin (25 mg/m^2) on days 1, 8 and 15 and docetaxel (20 mg/m^2) on days 1, 8 and 15 every 4 weeks. Docetaxel was infused over 30 min with 16 mg dexamethasone and 3 mg granisetron administered just before the docetaxel infusion. Ninety minutes after the completion of the docetaxel infusion, 25 mg/m^2 cisplatin were administered over 15 min with 1500 ml normal saline over 3.5 h. The prophylactic administration of G-CSF was not permitted. Administration of G-CSF was permitted in patients with grade 4 neutropenia and/or leukopenia or grade 3 febrile neutropenia. The administration of both cisplatin and docetaxel were skipped on day 8 and/or day 15 if the patients met the following criteria: WBC <2000/mm^3 and/or platelets <50 000/mm^3. No dose modifications were carried out on days 8 and/or day 15 of the cisplatin and docetaxel administrations. Treatment was carried out for at least two courses, unless unacceptable toxicity or disease progression occurred.

Response and toxicity evaluation

The patients' responses were evaluated according to the World Health Organization criteria [17]. A complete response (CR) was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks. A partial response (PR) was defined as a reduction of ≥50% in the product of the largest perpendicular diameters of one or more clearly measurable lesions or as a >50% reduction in evaluable malignant disease lasting for >4 weeks with no new areas of malignant disease. No change included: the regression of indicator lesions that were insufficient to meet the criteria for PR, <25% increase in any measurable lesion and no new lesions of malignant disease. Progressive disease was defined as an increase in any measurable lesion by >25% or a new lesion of malignant disease. Survival times from the start of treatment were calculated using the Kaplan–Meier method. The toxicity grading criteria of the Japan Clinical Oncology Group (JCOG) were used to evaluate toxicity [18]. Most detailed gradings for individual organ toxicity in the JCOG Toxicity Criteria are identical to those of the National Cancer Institute Common Toxicity Criteria proposed in 1988. The only differences in the definitions used in the present study were that neutrophils were used instead of granulocytes and the definitions for nausea and vomiting were combined.

Statistical analysis

According to the minimax two-stage phase II study design by Simon [19], the treatment program was designed to refuse response rates of 20% and to provide a significance level of 0.05 with a statistical power of 80% in assessing the activity of the regimen as a 40% response rate. The upper limit for first-stage drug rejection was four responses among 18 evaluable patients; the upper limit of second-stage rejection was 10 responses among 33 evaluable patients. Overall survival was defined as the interval between enrolment in this study and death or the last follow-up visit. Median overall survival was estimated using the Kaplan–Meier analysis method [20].

Results

Patient characteristics

Between February 2000 and March 2002, 34 elderly patients with NSCLC were enrolled and 33 were treated in this study (Table 1). One patient did not receive the protocol treatment because the PS of the patient decreased before the start of the treatment and the patient no longer met the eligibility criteria. All treated patients were assessed for response, survival and toxicity. The median age of the patients was 77 years (range 75–86). The gender, PS and histology of the patients were as follows: 26 males, seven females; seven patients with PS 0, 26 patients with PS 1; 20 patients with adenocarcinoma, nine patients with squamous cell carcinoma, three patients with large cell carcinoma and one patient with NSCLC. Twenty-four patients had no prior treatment, five patients had undergone surgery, three patients had received radiotherapy for brain and/or bone metastases, and one patient had undergone both surgery and radiotherapy as prior treatments.

Treatment received and dose intensity

The total number of treatment cycles was 101 and the median was 3 (range 1–15). Two patients received only one course because of a decrease in their PS. Of the 33 treated patients, 12 patients received two courses, 13 received three and six received four or more. One patient received 15 courses; however, he received

Table 1. Characteristics of treated patients

No. of entered patients	34
No. of treated patients	33
Sex	
Male	26
Female	7
Age (years)	
Median	77
Range	75–86
PS (ECOG)	
0	7
1	26
Histology	
Adenocarcinoma	20
Squamous-cell carcinoma	9
Large-cell carcinoma	3
Non-small-cell	1
Stage	
IIIA	1
IIIB	9
IIIB with effusion	3
IV	17
Relapse	6
Prior treatment	
None	24
Radiotherapy	4
Surgery	6

PS (ECOG): performance status (Eastern Cooperative Oncology Group).

treatments on only days 1 and 15 of the fifth to fifteenth courses. Between the first and fourth cycles, 77–100% of the patients received treatments on days 8 and 15 treatment (Table 2). Of the 303 planned administrations, 272 (90%) were carried out.

The median actual dose intensities of docetaxel and cisplatin were 13.4 mg/m^2 (range 8.9–16.4) and 16.7 mg/m^2 (range 11.1–20.4) per week, whereas the projected dose intensities were 15.0 and 18.8 mg/m^2 per week for docetaxel and cisplatin, respectively.

Objective tumor response and overall survival

The objective tumor response is shown in Table 3. Two CRs and 15 PRs occurred for an objective response rate of 52% (95% CI 31% to 67%) in 33 treated patients. The overall survival periods of all treated patients are shown in Figure 1. The median survival time of the 33 treated patients was 15.8 months with a median follow-up time for 11 censored patients of 18.1 (15.2–35.5) months. The 1-year and 2-year survival rates were 64% and 26%, respectively.

Table 2. Treatment received

No. of treatment cycles	No. of patients	Treatment received on	
		Day 8	Day 15
1	33	31 (94%)	32 (97%)
2	31	28 (90%)	24 (77%)
3	19	19 (100%)	17 (89%)
4	6	5 (83%)	5 (83%)
5	2	1 (50%)	1 (50%)

Toxicity

The worst grades of hematological and non-hematological toxicities experienced by each patient are listed in Table 4. Both hematological and non-hematological toxicities were relatively mild. No grade 4 hematological or non-hematological toxicities were observed. Only grade 3 leukopenia (6%), neutropenia (12%), anemia (3%), hyponatremia (3%) and nausea/vomiting (3%) were observed. None of the patients received G-CSF. Renal toxicity was also relatively mild: grade 2 renal toxicity was observed in only one of 33 patients.

Discussion

We previously reported that classic standard cisplatin-based chemotherapy regimens cause severe myelotoxicity in elderly patients aged ≥75 years [5]. Based on that previous study of elderly patients with NSCLC, we conducted phase I studies in which cisplatin and docetaxel were administered as three consecutive weekly infusions in both non-elderly and elderly patients with NSCLC using the same eligibility criteria, except for age, and the same definitions of dose-limiting toxicity and maximum-tolerated dose [15]. Our hypothesis was that the recommended dose for elderly patients aged ≥75 years would differ from that for non-elderly patients. In the previous phase I studies, we demonstrated a difference in the recommended dose of docetaxel combined with cisplatin between non-elderly and elderly patients [15]. The recommended doses of docetaxel with 25 mg/m^2 cisplatin were 35 and 20 mg/m^2 on days 1, 8 and 15 for non-elderly and elderly patients, respectively. We also conducted phase II studies for non-elderly and elderly patients with NSCLC using each recommended dose and the same eligibility criteria, except for age. The

Table 3. Response rate

No. of patients	CR	PR	NC	PD	NE	Response rate (95% CI)
33	2	15	13	2	1	52% (31% to 67%)

CI, confidence interval; CR, complete response; NC, no change; NE, not evaluable; PD, progressive disease; PR, partial response.

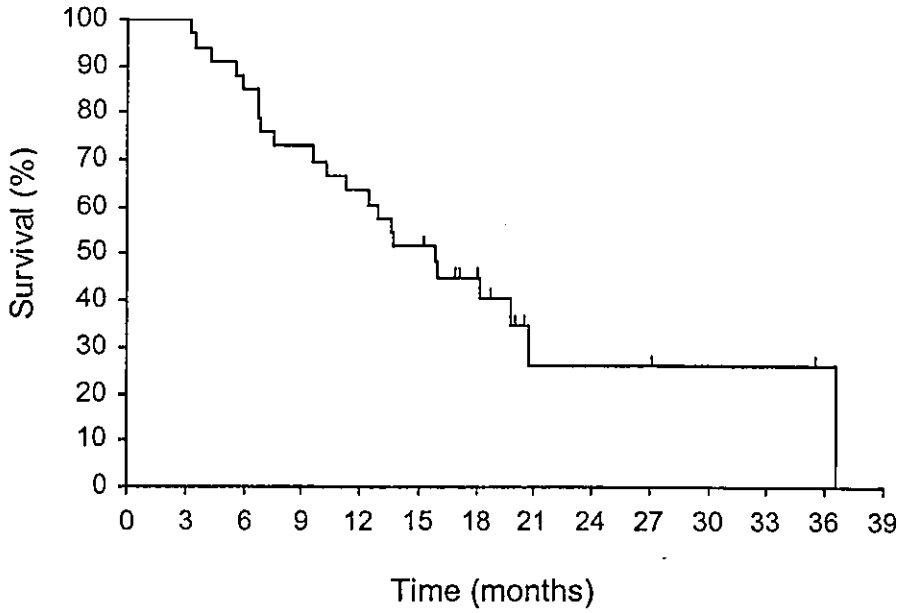

Figure 1. Overall survival time. The median survival time of the 33 treated patients was 15.8 months, and the median follow-up time for 11 censored patients was 18.1 (15.2–35.5) months. The 1-year and 2-year survival rates were 64% and 26%, respectively.

Table 4. Maximum toxicity grades associated with weekly docetaxel and cisplatin in 33 treated patients

	Grade (Japan Clinical Oncology Group)					Grade ≥3
	0	1	2	3	4	
Leukopenia	13	6	12	2	0	6%
Neutropenia	16	5	8	4	0	12%
Anemia	9	8	15	1	–	3%
Thrombocytopenia	30	2	1	0	0	0
Nausea/vomiting	12	10	10	1	–	3%
Hyponatremia	22	8	2	1	0	3%
Diarrhea	23	6	4	0	0	0
Infection	32	1	0	0	0	0
Fever	27	4	2	0	0	0
Bilirubin	25	–	8	0	0	0
Transaminase	25	8	0	0	0	0
Creatinine	28	4	1	0	0	0
Fatigue	26	6	1	0	0	0

results of the phase II study for non-elderly patients with NSCLC have been reported elsewhere [16]. Among the 33 evaluable patients, an objective tumor response of 30% (95% CI 15% to 46%) and a median survival time of 12.8 months were observed [16]. In the current study, we observed an objective tumor response of 52% (95% CI 31% to 67%) and a median survival time of 15.8 months for elderly patients with NSCLC. In spite of the lower dose of docetaxel, the efficacy of the treatment did not seem to be diminished.

Italian oncology groups have conducted randomized trials for elderly patients aged ≥70 years [21–23]. In these studies, non-platinum-based single or double chemotherapy regimens, such as vinorelbine alone or vinorelbine plus gemcitabine were used for elderly patients with NSCLC [21–23]. These chemotherapy regimens might not be adequate for non-elderly patients with a good PS because the cisplatin plus vinorelbine regimen was significantly superior to vinorelbine alone with regard to both the response rate and the survival [24, 25]. Kubota et al. [26] reported that the frequency of grade 4 leukocytopenia in the elderly (≥70 years of age) group was significantly greater than in the non-elderly group and that no difference in overall survival was observed between the two groups. Langer et al. [27] reported that advanced age alone

Table 5. Chemotherapy for elderly patients with non-small-cell lung cancer

Study	Chemotherapy	Age (years)	No. of patients	PS 2 (%)	Stage III (%)	RR (%)	MST
ELVIS [21]	None	≥70	78	24	28	–	21 weeks
	VNR 30 mg/m^2 days 1, 8 q3 weeks		76	24	26	20	28 weeks
	VNR 30 mg/m^2 days 1, 8 q3 weeks		233	19	29	18	36 weeks
MILES [22]	GEM 1200 mg/m^2 days 1, 8 q3 weeks	≥70	233	18	30	16	28 weeks
	GEM 1000 mg/m^2 + VNR 25 mg/m^2 days 1, 8 q3 weeks		232	19	31	21	30 weeks
SICOG [23]	VNR 30 mg/m^2 days 1, 8 q3 weeks	≥70	60	22	42	15	18 weeks
	GEM 1200 mg/m^2 + VNR 30 mg/m^2 days 1, 8 q3 weeks		60	27	40	22	29 weeks
MPCRN [29]	DTX 36 mg/m^2 weekly × 6 q8 weeks	≥65[a]	39	41	31	18	5 months
Current study	CDDP 25 mg/m^2 + DTX 20 mg/m^2 days 1, 8, 15 q4 weeks	≥75	33	0	29	52	15.8 months (69 weeks)

[a]Or poor candidates for combination chemotherapy due to coexistent medical illness.
ELVIS, The Elderly Lung Cancer Vinorelbine Italian Study; MILES, Multicenter Italian Lung Cancer in the Elderly Study; SICOG; Southern Italy Cooperative Oncology Group; MPCRN, Minnie Pearl Cancer Research Network.
CDDP, cisplatin; DTX, docetaxel; GEM, gemcitabine; VNR, vinorelbine.
MST, median survival time; PS, performance status; RR, response rate.

should not preclude appropriate NSCLC treatment, although elderly patients aged ≥70 years have more co-morbidities and can expect a higher incidence of leukopenia and neuropsychiatric toxicity. In the United States, upper age limits are not included in eligibility criteria to avoid age discrimination. In contrast, most Japanese studies have upper age limits because Japanese government guidelines recommend that elderly patients, >75 years, should not be accrued in common clinical trials [28]. This recommendation was made in concern for the safety of elderly patients. In Japan, most clinical trials include patients aged ≤74 years, and the full-dose chemotherapy is administered. Clinical trials for elderly patients have generally been conducted as specific trials focusing on the treatment of elderly patients in Japan. However, the definition of 'elderly' is still unclear. Thus, the use of platinum-based chemotherapy in elderly patients with NSCLC remains controversial because no randomized phase III studies have been conducted to resolve this question.

Several chemotherapy trials for elderly patients with NSCLC have been reported [21–23, 29] (Table 5). Of the subjects in these trials, 18–41% were PS 2 patients. Eligible patients were 70 or 65 years or older. The response rates of the non-platinum-based single or double chemotherapy regimens ranged from 15% to 22%, and the median survival times ranged from 18 to 36 weeks [21–23, 29]. In the current study, however, PS 2 patients were excluded and only patients aged ≥75 years were included. The objective response rate of 52% (95% CI 31% to 67%) and the median survival time of 15.8 months (69 weeks) in our trial were extremely better than those of previous trials. We considered that the main reason for the better results was the exclusion of PS 2 patients. However, cisplatin chemotherapy might be important not only for non-elderly, but also for elderly patients with NSCLC.

We divided the cisplatin and docetaxel dosages on days 1, 8 and 15 because full-dose cisplatin is too toxic for elderly patients. The weekly administration of docetaxel produces a higher dose intensity and less myelotoxicity [12–14]. Moreover, a weekly schedule may be safer than a 3-weekly schedule because treatment on day 8 and/or day 15 can be omitted if severe toxicity is observed. In the current study, the toxicity, including nausea/vomiting and renal toxicity, was relatively mild, and 90% of the planned administrations were carried out. The dose-limiting toxicities of docetaxel administered in six consecutive weekly infusions were reported to be fatigue and asthenia [12–14]. In the previous phase I study, two out of six patients refused chemotherapy on day 15 because of fatigue and asthenia at level 2: 25 mg/m^2 cisplatin and 25 mg/m^2 docetaxel [15]. However, fatigue and asthenia were relatively mild in the current study because of the relatively low-dose of docetaxel (20 mg/m^2).

We conclude that cisplatin and docetaxel administered as three consecutive weekly infusions is very effective and safe for elderly patients with chemotherapy-naive NSCLC. The JCOG is conducting a phase III study of cisplatin and docetaxel versus docetaxel alone, administered as three consecutive weekly infusions, for elderly patients with NSCLC to examine the role of cisplatin in the treatment of elderly patients with NSCLC.

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Genome-wide cDNA microarray screening to correlate gene expression profile with survival in patients with advanced lung cancer

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Abstract. We conducted a study using cDNA microarray analysis to determine whether expression levels of genes in tumors were correlated with survival after chemotherapy. Between September 2000 and December 2001, 47 patients were registered in the study. Eighteen patients had small cell lung cancer (SCLC), and the others had non-small cell lung cancer (NSCLC). All patients except three received platinum-based chemotherapy. Transbroncheal biopsy specimens of tumors were obtained before chemotherapy. The expression levels of 1176 genes in tumor specimens were analyzed using the Atlas™ Human Cancer 1.2 Array. The expression levels of three genes, G1/S-specific cyclin, type II cGMP-dependent protein kinase and hepatocyte growth factor-like protein, were significantly correlated with survival ($p<0.01$). Ten of the 47 patients who showed an elevated expression level of one or more of the three genes had a significantly increased chance of survival ($p=0.0056$). In conclusion, some survival-related genes were detected in the tumor tissue of lung cancer patients using cDNA microarray analysis. A prospective study is required to confirm whether expression levels of these genes can be used for prognosis.

Introduction

Lung cancer is a leading cause of cancer death and most patients with this disease are candidates for chemotherapy. To improve the prognosis of lung cancer patients, attempts have been made to develop treatment of lung cancer and thereby decrease the mortality from this disease. To develop new therapeutic strategies for lung cancer we require a better understanding of the cell biology of this disease. Although a number of clinicopathological characteristics may affect the prognosis of lung cancer, these characteristics have not yet been defined. Several molecular markers have been evaluated in association with established histological and clinical prognostic parameters of non-small cell lung cancer (NSCLC) (1-5), although the intrinsic nature of gene dysregulation that leads small tumors to metastasize remains unclear. It is suspected that tumor invasion and metastasis involve complex alterations of gene expression that may be selective for specific cancer types.

We identified that survivin and cyclin D1 are indicators of poor prognosis in small adenocarcinoma of the lung (6,7). Moreover, other factors have also been reported to be prognostic factors in resected NSCLC, including cyclin E (1), FHIT (2), VEGF (3), cadherin (4) and RAR-ß (5). These factors have different functions in tumors, such as tumor suppression, angiogenesis, apoptosis, adhesion and cell differentiation. Clarification of the many genetic abnormalities that influence tumor progression in NSCLC is clearly required when considering new therapeutic strategies for resectable NSCLC.

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 genome-wide expression profiles that can generate a large body of information concerning genetic networks related to pathological conditions. Large-scale gene expression microarray studies of lung cancer have shown that expression patterns of various genes is associated with pathological characteristics (8,9). In other studies, different sets of genes were identified which may act as predictive markers for chemosensitivity to drugs in human cancer cell lines or tumor tissues using cDNA microarray (10-12).

In the present study, we used cDNA microarray screening to examine the expression levels of specific genes in tumor tissue obtained by transbroncheal biopsy, in order to determine any correlations with survival after chemotherapy.

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Key words: microarray, lung cancer

Patients and methods

Patients. This study was approved by the Institutional Review Boards of Kanagawa Cancer Center. The patients with histologically proven lung cancer treated with chemotherapy were entered into the present study. All were eligible for treatment. They had an expected survival of at least six weeks; measurable lesions; Eastern Cooperative Oncology Group performance status (PS) score ≤3; white blood count ≥4000/μl; hemoglobin ≥10 g/dl; platelet count ≥100000/μl; total serum bilirubin <2 mg/dl; aspartate aminotransferase and alanine aminotransferase less than twice the upper limit of the normal range; serum creatinine ≤1.5 mg/dl; and creatinine clearance >50 ml/min. None of the patients had received prior chemotherapy for the primary lesion. Written informed consent for chemotherapy and a genetic analysis of tumor tissue was obtained in every case. All patients with non-progressive cancer were treated with two or more courses of chemotherapy.

Tumor samples. Transbroncheal biopsy specimens of tumors were obtained before chemotherapy. One half of the specimens were fixed in formalin for pathological diagnosis and the other half were immediately frozen for storage at -80°C until genetic analysis.

Extraction and purification of RNA and preparation of probes. The total RNA of each sample was isolated and treated with DNaseI to avoid contamination of genomic DNA by silica membrane affinity chromatography using Macherey-Nagel's total RNA isolation kit (Macherey-Nagel GmbH and Co., KG, Germany). Total RNA (100 nanograms) for each sample was reverse transcribed into cDNA and amplified by SMART polymerase chain reaction (PCR) technology (18) using the Super SMART™ PCR cDNA Synthesis kit (BD Biosciences Clontech, CA, USA) according to the manufacturer's instructions. To represent the expression profile of the initial total RNA material, the optimal conditions for PCR cycling were determined for each sample by testing the amplified cDNA with gel electrophoresis. All samples were amplified for 19 to 23 cycles. Each cDNA sample was subjected to microarray expression profiling using the BD Atlas™ Human Cancer 1.2 Array (Clontech) based on the manufacturer's protocol. The following is a brief overview of the procedures used. A radioactively labeled probe mixture for hybridization with array membranes was synthesized from each cDNA sample using the CDS Primer Mix specific for the Atlas™ Human Cancer 1.2 Array and [α-^{32}P]-dATP.

cDNA microarray. Each labeled probe was hybridized into a separate Atlas Array. After appropriate washing, array membranes were exposed to a phosphor screen and the signal intensity for each spot, which corresponds to each gene examined, was determined using a STORM image analyzer (Amersham Bioscience, Picataway, NJ). The hybridization pattern and signal intensity were analyzed to determine changes in gene expression levels using AtlasImage™ 2.01 software (Clontech, Laboratory, Inc., Japan).

Table I. Patient characteristics.

	No. of patients
Total	47
Gender	
Male	36
Female	11
Smoker	38
PS (ECOG)	
0	5
1	30
2	9
3	3
Pathology	
SCLC	
Stage	
LD	2
ED	16
NSCLC	
Stage	
IIB/IIIA	4
IIIB	8
IV	17

PS, performance status; ECOG, Eastern Cooperative Oncology Group; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; LD, limited disease; ED, extensive disease.

Statistical methods. To determine whether gene-expression profiles were associated with variety in cases of survival, Kaplan-Meier survival plots and log-rank tests were used. $p<0.01$ was considered statistically significant.

Results

Between September 2000 and December 2001, 47 patients were registered in the study. Patient characteristics are summarized in Table I. Thirty-six patients were male and eleven were female, with a median age of 66 years (range 35-81 years). Thirty-eight patients were smokers. The PS was 0 for five patients; 1 for 30 patients; 2 for nine and 3 for three patients. Eighteen patients had small cell lung cancer (SCLC), and the remaining had NSCLC. Of the patients with SCLC, two had limited disease and the other 16 had extensive SCLC. Of the patients with NSCLC, four had stage IIB/IIIA, eight had stage IIIB, and 17 had stage IV. None of the patients had received prior chemotherapy.

All patients except three who had been subscribed paclitaxel and irinotecan were given platinum-based chemotherapy. Three patients with SCLC and seven patients with NSCLC received thoracic radiotherapy concurrently or sequentially with chemotherapy (Table II). Sixteen of the 18 patients with SCLC (89%) and 12 of the 29 patients with NSCLC (41%) responded to chemotherapy, respectively. Eight out of the total 47 patients were alive at analysis.

Table II. Therapeutic regimens.

	No. of patients
SCLC	
Cisplatin + etoposide	6
Cisplatin + etoposide + TRT	2
Cisplatin + irinotecan	4
Cisplatin + irinotecan + etoposide	2
Carboplatin + etoposide	3
Cisplatin + TRT	1
NSCLC	
Cisplatin + gemcitabine	7
Cisplatin + vinorelbine	3
Cisplatin + vinorelbine + TRT	2
Cisplatin + vindesine + TRT	3
Cisplatin + irinotecan	1
Cisplatin +TRT	2
Carboplatin + etoposide	1
Carboplatin + paclitaxel	1
Nedaplatin + irinotecan	6
Paclitaxel + irinotecan	3

SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; TRT, thoracic radiation therapy.

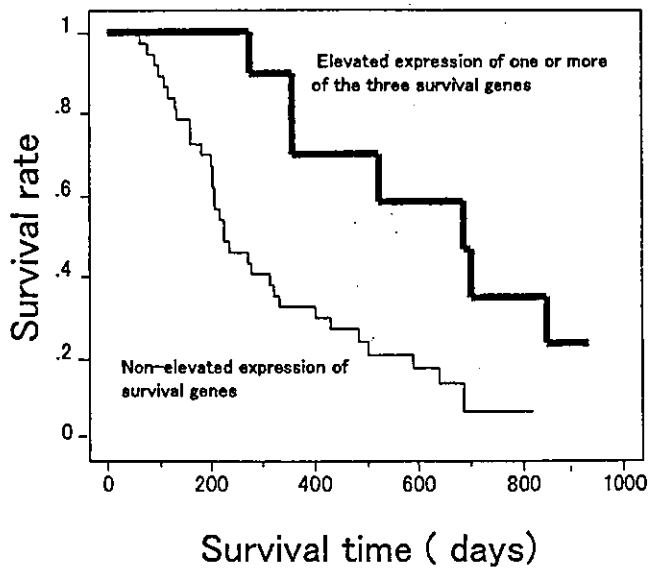

Figure 1. Survival curves constructed using the Kaplan-Meier method. Ten of 47 patients who showed an elevated expression of one or more of the three survival genes compared to the mean expression level of control genes had a significantly better chance of survival (log-rank, p=0.0056).

The expression levels of 1176 genes in the tumor specimens were analyzed using cDNA microarray screening. Four housekeeping genes which were expressed in all 47 tumor samples in the present study were used as controls for gene expression: ubiquitin, liver glyceraldehydes 3-phosphate dehydrogenase, 23-kDa highly basic protein, 60S ribosomal protein L13A and 40S ribosomal protein S9.

When we analyzed the relationship between gene expression level and survival, three genes, G1/S-specific cyclin, type II cGMP-dependent protein kinase and hepatocyte growth factor-like protein, were significantly correlated (Table III, log-rank test, $p<0.01$). Ten of 47 patients who showed an elevated expression of one or more of the three survival genes compared to the mean expression level of control genes had a significantly better chance of survival (Fig. 1, log-rank; p=0.0056).

Discussion

We examined cancer-related gene expressions in lung cancer samples obtained before chemotherapy using cDNA microarray screening, and analyzed the relationship between gene expression levels and survival after chemotherapy. We identified three genes whose expression could be used to predict the survival outcomes of patients in the present study. These genes were involved in cell cycling, adhesion and invasion. The families of G1-cyclins such as cyclins D and E, and their dependent kinases, control the transition through the restriction point of the middle and late G1 cells during cell cycles. A previous examination of gastric cancers revealed that positivity of cyclin D2 and negativity for p27 in the tumor tissue were independent of prognostic factors (13).

For cancer to metastasize, tumor cells present in the circulation must first adhere to the endothelium. An

Table III. Genes closely associated with patient survival.

Description	Symbol	p-value
G1/S-specific cyclin D2 (CCND2) + KIAK0002	M90813 + D13639	0.0055
Type II cGMP-dependent protein kinase	X94612	0.0016
Hepatocyte growth factor-like protein (HGF activator-like protein); hyaluronan-binding protein (PHBP)	D49742, S83182	0.0075

investigation of the mechanism of adhesion and trans-endothelial migration of cancer cells showed that stimulation of cancer cells by CD44 cross-linking or fragmented hyaluronan markedly induces the expression of lymphocyte function-associated antigen (LFA)-1; that stimulation of CD44 also induces expression of the hepatocyte growth factor (HGF) receptor c-Met on cancer cells; and that HGF further amplifies the LFA-1-mediated adhesion of cells (14). Another study demonstrated that HGF/SF-Met binding up-regulated the expression of CD44v6 in murine melanoma cells (15). These data support the hypothesis that HGF influences the outcome of patient survival.

Tumor hypoxia is associated with a poor prognosis for patients with various cancers, often resulting in an increased metastasis. A study demonstrated that culturing tumor cells under hypoxic conditions results in lower cyclic GMP levels. The study revealed that an important mechanism by which hypoxia increases tumor cell invasiveness requires inhibition of the nitric oxide signaling pathway involving protein kinase G activation (16). Moreover, in another study, a potent inhibitor of cyclic GMP-dependent protein kinase displayed cytostatic activity against *Toxoplasma gondii in vitro* (17). These data may support the hypothesis that the three survival genes identified in this study do influence the outcome of patient survival.

In this report we have discussed the mechanisms related to tumor cell survival with regard to three genes implicated in patient survival outcomes. We need to undertake prospective evaluations to determine whether the selected genes in this study are truly important and potentially useful for predicting patient survival. It is also necessary to determine whether administration of drugs will result in changes to the expression levels of the survival genes we identified, and if any such changes are related to survival. If the expression level of a gene changes with treatment, that gene will be the new target of cancer chemotherapy. In this study we measured the expression levels of genes in patients treated with platinum-based chemotherapy. Recently, patients with NSCLC have been treated with non-platinum chemotherapy. It is thus also necessary that the expression levels of our survival genes can be used to predict clinical outcome with non-platinum chemo-therapy. Accumulation of these data could eventually lead to the prescription of 'personalized chemotherapy' with effective anticancer drugs.

Acknowledgements

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SHORT COMMUNICATION

Phase II study of OK-432 intrapleural administration followed by systemic cisplatin and gemcitabine for non-small cell lung cancer with pleuritis carcinomatosa*

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We conducted a phase II study of OK-432 intrapleural administration followed by systemic chemotherapy using cisplatin with gemcitabine to determine their combined effects on non-small cell lung cancer (NSCLC) with pleuritis carcinomatosa. Between December 1999 and October 2001, 15 patients were registered in the study. Fourteen patients had an Eastern Cooperative Oncology Group performance status (PS) of 1, and one patient had a PS of 2. Ten patients had adenocarcinoma, one had squamous cell carcinoma, and four had malignant mesothelioma. Patients underwent thoracocentesis and received an OK-432 intrapleural injection. They were then treated every three weeks with chemotherapy consisting of 80 mg/m2 cisplatin on day 1 and 1000 mg/m2 gemcitabine on days 1 and 8. Thirteen patients received two or more courses of chemotherapy. Grade 3 or 4 neutropenia, anemia and thrombocytopenia occurred in five, two and three patients, respectively. Non-hematological toxicities were mild, except for one patient who experienced a grade 3 elevation of transaminase and two patients who experienced grade 3 nausea. Of the 15 patients, one achieved partial response (PR), 13 a stable disease (SD) rating, and one a progressive disease (PD) rating, and the overall response rate was 6.7%. The median survival time was 13.5 months and the one-year survival rate was 60.0%. In conclusion, OK-432 intrapleural administration followed by cisplatin and gemcitabine systemic chemotherapy did not reduce patients' tumors but did prolong their survival time. A large-scale phase II study of the efficacy of this combination therapy is required.

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INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death in Japan. To improve the prognosis of lung cancer patients, attempts have been made to develop tests that will facilitate the early diagnosis and treatment of lung cancer and thereby decrease the mortality from this disease. Pleuritis carcinomatosa is one type of advanced stage NSCLC, and shows poor prognosis due to micrometastatic lesions and respiratory failure by massive pleural effusion. Standard therapy for NSCLC with pleuritis carcinomatosa consists of drainage of pleural effusion followed by intrapleural administration of sclerosing agents. Until recently, there has been controversy regarding which agent was most effective for treatment of sclerosing pleural lesions. A randomized phase II study has been conducted to compare three regimens for intrapleural treatment in patients with pleuritis

carcinomatosa of NSCLC (1). The study suggested that intrapleural OK-432 administration was more effective for the management of malignant effusion compared to intrapleural administration of bleomycin or cisplatin plus etoposide.

Systemic chemotherapy is usually performed after sclerosing modality treatment for patients. In the past decade, a number of new anti-cancer agents have been approved for the treatment of advanced NSCLC, including vinorelbine, gemcitabine, docetaxel and paclitaxel. Regimens based on the combination of these drugs with platinum compounds have presented interesting new possibilities for treatment of patients with NSCLC. Randomized studies comparing these platinum-based combinations with single-agent treatment have demonstrated a small but significant survival benefit with the combination treatments (2, 3). The treatment for NSCLC with pleuritis carcinomatosa, usually performed in accordance with the chemotherapy regime for metastatic NSCLC, is controversial. A phase II study of cisplatin and gemcitabine combination chemotherapy, one of the standard therapies for metastatic NSCLC, has been conducted to determine its effects on malignant mesothelioma (4). The study reported 10 responders out of the 21 patients treated, and a median survival time of 41 weeks, suggesting an efficacy of cisplatin and gemcitabine for treating malignant pleural lesions of NSCLC.

With reference to these data, we conducted a phase II study to determine the efficacy of intrapleural administration of OK-432 followed by cisplatin and gemcitabine systemic chemotherapy for the treatment of NSCLC with pleuritis carcinomatosa. For this study, we used a gemcitabine and cisplatin regimen with a 21-day schedule. In previous phase II studies, based on a 28-day cycle, gemcitabine was given at a dose of 1000 mg/m^2 on days 1, 8 and 15 (5, 6). However, the number of omissions and reductions of the day-15 gemcitabine dose was quite high. As a previous study has shown that cisplatin and gemcitabine treatment on a 21-day cycle has a high-dose intensity with high activity (7), we chose a 21-day cycle of this combination chemotherapy for the present study. This study allowed the entry of patients with malignant mesothelioma.

PATIENTS AND METHODS

Patients

Patients with histologically or cytologically diagnosed NSCLC with pleuritis carcinomatosa or malignant mesothelioma were registered for intrapleural therapy using OK-432 followed by cisplatin and gemcitabine systemic chemotherapy. The eligibility criteria were: expected survival time ≥6 weeks, age ≦ 75 years, Eastern Cooperative Oncology Group performance status (PS) score ≤1, leukocyte count ≥4,000/μl, hemoglobin count ≥10 g/dl, platelet count ≥100,000/μl, total serum bilirubin ≤1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase ≤90 IU/L, serum creatinine ≤1.5 mg/dL, and creatinine clearance ≥60 ml/min. Patients who had already received radiotherapy to their metastatic sites were not eligible for the present study. Written informed consent was obtained from every patient.

Treatment

Patients underwent thoracocentesis, and a 19-Fr chest drainage tube was kept in place until the drained volume of pleural effusion was less than 100 ml/day. Then, a 5–10 Klinische Einheit unit of OK-432 diluted by 100 ml saline was administered into the pleural cavity. The chest tube was clamped for 1–3 hours and then released for drainage. When the drained effusion volume was less than 100 ml/day, the chest tube was removed. Following intrapleural therapy, patients were treated every three weeks with two or more courses of systemic chemotherapy consisting of 80 mg/m^2 cisplatin on day 1 and 1000 mg/m^2 gemcitabine on days 1 and 8. Subsequent courses of chemotherapy were started when the leukocyte count was ≧ 4000 /μL, with a platelet count ≧ 100,000 /μL. The dose of gemcitabine was reduced to 800 mg/m^2 for the subsequent course if the patient experienced grade 4 thrombocytopenia, or grade 4 neutropenia lasting four days. Physical examination, complete blood cell counts, biochemical tests, and chest roentgenograms were obtained weekly. Tumor responses were evaluated according to the Response Evaluation Criteria for Solid Tumors (8). Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC Version 2.0).

Fifteen patients were treated in the first stage. We decided to stop the study if less than three of the 15 patients responded at this stage. If four or more patients responded, a total of 26 patients would be required. This regimen was defined as active if the number of responders was ≧ 10 and inactive if the number of responders was ≦ 9 (Simon minimax two stage; α <0.05 and β< 0.10) (9, 10). This plan allowed early termination of the study as soon as possible should it become evident that the true rate of response was less than 25% or greater than 45%. Overall survival time was estimated using the method devised by Kaplan and Meier. The Review Board of the Kanagawa Cancer Center reviewed and approved the protocol prior to commencement of the trial.

Table 1. *Patient characteristic.*

			No. of patients
Total			15
Age, years	Median		62
	Range		29 - 74
Gender	Male		10
	Female		5
Performance status		1	14
(ECOG)		2	1
Histology	Adenocarcinoma		10
	Squamous cell carcinoma		1
	Mesothelioma		4
No. ofmetastatic sites		0	10
		1	5

RESULTS

Between December 1999 and October 2001, 15 patients were registered in the study. Patient characteristics are summarized in Table 1. Ten patients were male and five were female, with a median age of 62 years (ranging from 29 to 74). Fourteen patients had a PS of 1 and one patient had a PS of 2. Ten patients had adenocarcinoma, one had squamous cell carcinoma, and four had malignant mesothelioma. No patients had received prior treatment, including any radiotherapy for metastatic lesions. All fifteen patients were assessed for their response and for toxicities. Thirteen patients received two or more courses of chemotherapy. Two patients were not given a second course of chemotherapy, one because of PD, and another because of no improvement from a depressed PS 3.

Patients' hematologic and non-hematologic toxicities are summarized in Table 2. Grade 3 or 4 neutropenia, anemia and thrombocytopenia occurred in five (33%,), two (13%) and three (20%) patients, respectively. Non-hematological toxicities were mild, except in one patient, who experienced a grade 3 elevation of transaminase, and in two patients who experienced grade 3 nausea.

The outcome of chemotherapy in 15 patients with measurable lesions is shown in Table 3. One patient achieved a PR, 13 an SD, and one a PD, and the overall response rate was 6.7%. As only one patient responded, no further patients were registered for the first stage. The overall survival curve is shown in Figure 1. The median potential follow-up time was 18.5 months (range, 10.1–34.4), and the median time to progression (MTP) was 3.7 months (range, 1.9–11.2). Four patients were still alive and the other 11 patients died during the follow-up period. The median survival time (MST) was 13.5 months and the one-year survival rate was 60.0%.

Table 2. *Toxicities*

	No. of patients with Toxicity NCI-CTC ver.2 grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Hemoblobin	0	8	5	2	0
Leukocytes	2	2	8	3	0
Neutrophils	2	2	6	3	2
Platelets	4	5	3	3	0
Bilirubin	14	0	1	0	0
AST	8	5	1	1	0
ALT	7	5	2	1	0
Creatinine	14	1	0	0	0
Nausea	4	5	4	2	0
Vomiting	9	0	5	1	0
Phlebitis	14	0	1	0	0
Headache	14	1	0	0	0
Weight loss	12	3	0	0	0
Stomototis	14	1	0	0	0

Table 3. *Chemotherapeutic response.*

Responce	Number of Patients
PR	1
NC	13
PD	1

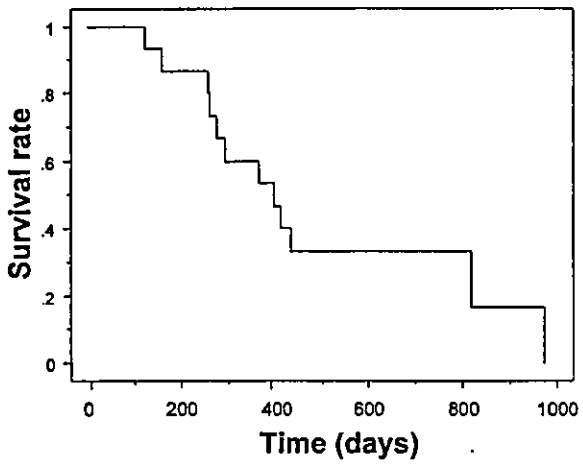

Figure 1. Kaplan-Meier estimation of overall survival of 15 patients with NSCLC with pleuritis carcinomatosa treated with cisplatin plus gemcitabine.

DISCUSSION

An effective treatment for NSCLC with pleuritis carcinomatosa has not been established. Sufferers usually experience massive pleural effusion and require pleurodesis before systemic chemotherapy. A randomized study conducted by the JCOG demonstrated the efficiency of intrapleural injection of OK-432 compared to bleomycin or cisplatin plus etoposide (1). Thirty-four patients in the study who received intrapleural treatment of OK-432 showed 28 weeks of median pleural progression-free survival and 48 weeks of MST. As these survival data were promising compared to those obtained with other treatments, we selected OK-432 administration for treating sclerosing pleural lesions in our study. Use of systemic chemotherapy after pleurodesis is also controversial, and the patients with pleuritis carcinomatosa are usually treated in accordance with the chemotherapy regimen for metastatic NSCLC. A large-scale, phase III study demonstrated an equal efficiency of cisplatin plus gemcitabine compared to cisplatin plus docetaxel, cisplatin plus paclitaxel, or carboplatin plus paclitaxel (11). We selected cisplatin plus gemcitabine for the treatment of pleuritis carcinomatosa after pleurodesis because the regimen was effective for malignant mesothelioma (4). Both pleuritis carcinomatosa and mesothelioma are pleural lesions, and the effective treatment for malignant mesothelioma is considered to also be effective for pleuritis carcinomatosa. It is also expected that cisplatin and gemcitabine shift to the thoracic cavity.

Unfortunately, only one patient responded to the combination of cisplatin and gemcitabine, so we terminated our study in the first stage. However, it should be noted that nine of the fifteen patients (60%) who entered our study survived over one year. While a combination of cisplatin and gemcitabine is one of the standard chemotherapies for advanced NSCLC, previous researchers have reported an MST of less than one year (5, 6, 11). Whether a measurable response is a good substitute for an increased survival time in the treatment of advanced cancer is still a matter of controversy (12). The survival time data in our study could not be confirmed as an outcome of treatment for pleuritis carcinomatosa because of the small number of patients analyzed, however it may suggest this combined therapy has potential for treatment of pleuritis carcinomatosa. Cisplatin and gemcitabine treatment induced a response rate similar to that of other standard chemotherapies in a randomized study against advanced NSCLC (11). The data showed that cisplatin and gemcitabine had a cytotoxic but not a cytostatic effect. The MTP was 3.7 months in our study, which is similar to other active regimens (11) and is considered to be long in spite of the poor response rate. The MTP is a measure of the quality of response, taking into account both objective response and stable disease qualifications. The reason why a good survival time was obtained in our study could not be explained; a tumor-stabilizing effect was certainly achieved with the treatment.

The JCOG study demonstrated that intrapleural sclerosing modality treatment using OK-432 is promising compared to intrapleural injection of anti-cancer agents such as bleomycin or cisplatin plus etoposide (1). OK-432 is not a cytotoxic agent and is used to achieve asclerosing effect for pleuritis carcinomatosa in Japan. The non-shrinking agent is more effective than cytotoxic agents for prolonging the survival of patients with lung cancer and pleuritis carcinomatosa, suggesting that stabilization of pleural lesions is most important for treatment of pleuritis carcinomatosa. OK-432 intrapleural administration followed by cisplatin and gemcitabine systemic chemotherapy did not reduce the tumor size in this study, but only one patient experienced tumor progression during the treatment. Chemotherapy regimens with a poor response rate usually have a 20–30% progression response and, therefore, the treatment used in this study may have the potential to stabilize pleural lesions and prolong survival.

We terminated this study in the first stage because of the poor response rate. In order to confirm the efficacy of OK-432 intrapleural administration followed by systemic chemotherapy with cisplatin and gemcitabine against pleuritis carcinomatosa, a large trial with survival time as the primary end-point is required.

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