TABLE 2. Characteristics of Patients with Advanced Invasive Thymoma

Patient No.	Age (yr)	Sex	Histology	Disease Stage	Site of Disease
1	40	M	B2	IVa	Pleural dissemination
2	59	F	B2	IVa	Pericardial effusion, pericardium, aorta, lung
3	72	M	B2	IVa	Pericardial effusion, pericardium, SVC, lung
4	63	M	B2	IVb	Mediastinal lymph nodes, pleural effusion
5	38	F	B2	III	SVC
6	33	M	B2	IVa	Pleural dissemination, lung
7	65	F	B2	IVb (rec)	Pulmonary metastasis, pleural dissemination
8	66	F	B2	IVb (rec)	Pulmonary metastasis
9	62	F	B2	III	SVC
10	56	M	B3	IVa (rec)	Pleural dissemination
11	29	M	B2	IVa	Pleural dissemination, pericardium, lung
12	49	M	B3	IVa	Pleural dissemination, pericardium, pulmonary artery
13	51	F	B2	III	SVC, lung
14	62	F	B3	IVa	Pleural dissemination
15	25	M	B2	IVa (rec)	Pleural dissemination
16	29	M	B2	IVb	Pulmonary metastasis
17	62	F	B2	III	SVC

Rec, recurrent case; SVC, superior vena cava.

TABLE 3. Summary of Treatments

Patient No.	Previous Treatment	Cycles of CAMP Therapy	Response to CAMP Therapy	Subsequent Treatment	Total Response	Sites of Tumor Progression	Progression-Free Survival (mo)	Treatment for Recurrences	Overall Survival (mo)
1	S (R2)	4	NA		CR	Pleura	61	S (R0)	193+
2	S (R2)	4	NA	RT	CR		180		180+
3		4	PR	S (R1), CAMP × 2, RT	CR	Pleura, lung	45	RT	180+
4		4	PR	S (R2), RT	PR	Pericardium	11	CT[1]	13
5		4	PR	S (R0), RT	CR		169		169+
6		2+CT[2]	PR	S (R2), RT	PR	Pleura	17	CT[2]	18
7		2	PR		PR		2		2
8		3	CR		CR	Pulmonary metastasis	7	S (R0)	88+
9		2	NC	S (R2), RT	PR	Primary site	42	RT	72+
10		4	PR	RT	CR	Pleura	32	RT	67+
11	S (R2)	4	NA		CR	Pleura	24	CAMP × 2, S (R0)	56+
12		4	PR	RT	PR		54		54+
13		4	PR	S (R0)	CR		43		43+
14		4	PR	S (R2), RT	CR	Pleura	23	CAMP × 4	37+
15		4	PR		PR	Pleura	18	CAMP × 4, S (R0)	29+
16		4	PR	S (R2), RT	CR		9		9+
17		4	PR	S (R2), RT	PR		6		6+

CR, complete remission; CT[1], CDDP+VLB+BLM; CT[2], CPA+ADM+VCR+prednisone; NA, not assessable; NC, no change; PR, partial remission; R0, complete resection; R1, microscopically incomplete resection; R2, macroscopically incomplete resection; RT, radiation therapy; S, surgery.

thymectomy combined with a partial resection of the pericardium, parietal pleura, and/or lung. Even after the resection, patients 1 and 11 retained numerous miliary pleural tumors in the hemithorax, and patient 2, with malignant pericardial effusion, had a residual mass on the aortic arch. These patients received four cycles of CAMP therapy after surgery, and only patient 2 underwent subsequent whole mediastinal radiation therapy.

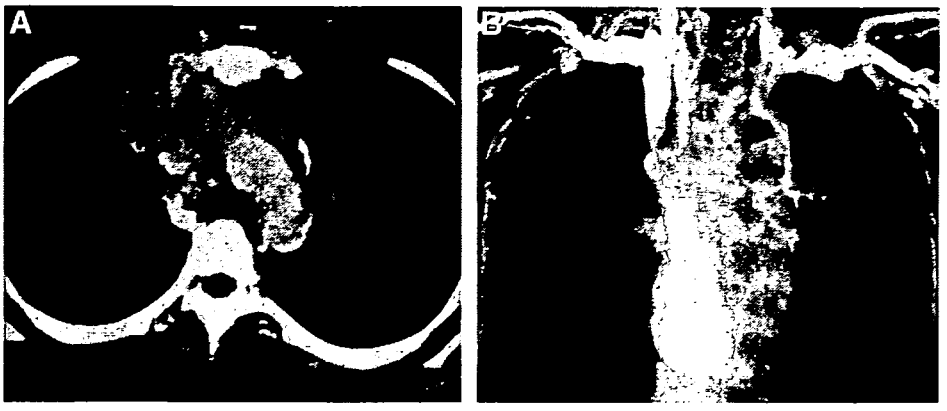

FIGURE 1. Patient 5 before chemotherapy. (*A*) CT scan showing a large anterior mediastinal tumor invading the superior vena cava. (*B*) Venous phlebogram illustrating an almost complete obstruction of the superior vena cava at the level of the junction of bilateral brachiocephalic veins.

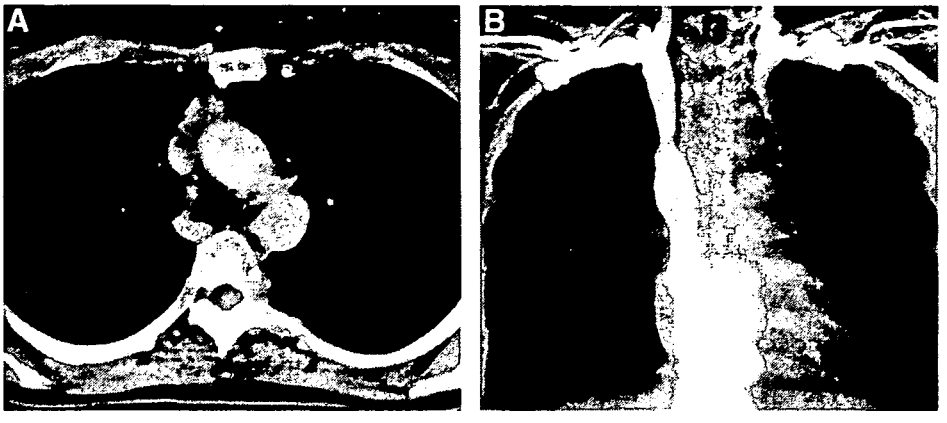

FIGURE 2. Patient 5 after four cycles of induction chemotherapy. (*A*) CT scan revealing considerable shrinkage of the tumor. (*B*) Venous phlebogram demonstrating the marked improvement of superior vena cava obstruction.

After completion of the multimodality therapy, 10 patients achieved CR and seven achieved PR; the overall remission rate was 100%. Tumor progression after treatment was observed in six (60%) of 10 CR patients and in four (57%) of seven PR patients, with a median progression-free survival of 24 months (range, 7–61 mo). The remaining six patients (four CR patients and two PR patients), 35% of the total population, had no tumor progression six to 180 months after the initiation of the multimodality therapy.

Treatment for recurrences was performed in all 10 patients. Complete surgical resection for the recurrences with or without preoperative CAMP therapy was accomplished in four patients. Patients 1 and 15 underwent an extrapleural pneumonectomy for pleural dissemination. Patient 8, who had recurrence after extrapleural pneumonectomy for the primary tumor, had a wedge lung resection for pulmonary metastasis, and patient 11 received a partial pleurectomy. For patients with unresectable recurrent tumors, radiotherapy was performed in three patients, and chemotherapy was performed in three patients whose tumors were unsuitable for radiotherapy. Two of the patients treated with chemotherapy died during the retreatment, one from recurrent tumor and the other from fulminant rhabdomyolysis.[18]

The 5- and 10-year overall survival rates of all patients were both 80.7% (95% CI, 60.9–100%) (Fig. 3). The survival curves according to stages of disease are shown in Figure 4. The 10-year survival rates of patients with stage III and stage IVa disease were 100 and 88.9% (95% CI, 68.4–100%), respectively. In stage IVb, the 5-year survival rate was 37.5% (95% CI, 0–93.6%), and only patient 8 survived for more than 5 years after CAMP therapy and resection for recurrence. In the 10 patients with recurrence, the median survival time and 5-year survival rate after retreatment were 30 months (range, 1–132 mo) and 30.0% (95% CI, 1.6–58.4%), respectively.

Toxicity of CAMP Therapy and the Multidisciplinary Treatment

The side effects of CAMP therapy are shown in Table 4. Seventy-one cycles were administered (median, four cycles;

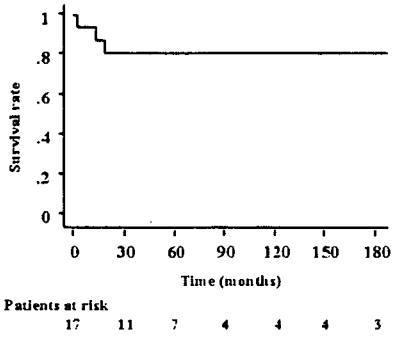

FIGURE 3. Overall survival of patients with advanced invasive thymoma who were treated with the multimodality therapy.

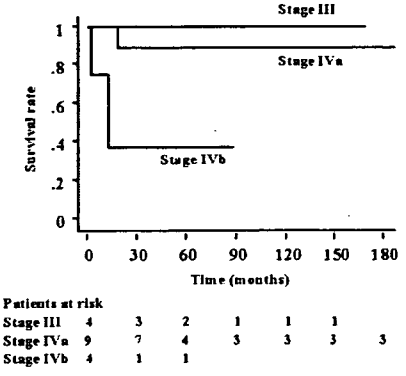

FIGURE 4. Survival according to the Masaoka staging system. In univariate analysis, there was a significant difference between stage IVa and stage IVb disease ($p = 0.036$), but there were no significant differences between stage III and stage IVa disease ($p = 0.564$) and stage III and IVb disease ($p = 0.123$).

TABLE 4. Toxic Effects of Cisplatin, Doxorubicin, and Methylprednisolone Therapy

NCI-CTC grade (%)	0	1	2	3	4	5
Leukocytes	14	12	39	27	8	
Neutrophils	10	9	21	34	26	
Hemoglobin	75	12	11	3		
Platelets	55	36	6	3		
Nausea/vomiting	31	26	36	5	1	
Infection	92	3		3	1	1

range, two to eight cycles), and the major adverse effects were leukopenia and neutropenia. Although 60% of cycles were associated with grade 3 or 4 neutropenia, almost all patients in the study received no granulocyte colony stimulating factors or no dose reduction of all three drugs. Treatment delays (median, 1 wk; range, 1–6 wk) were performed in eight patients because of neutropenia and patients' wishes. Chemotherapy-related death occurred in patient 7. She had multiple pulmonary metastases and pleural recurrences complicated with myasthenia gravis, pure red cell aplasia, and hypogammaglobulinemia. She died of pneumonia after the second cycle. Another peculiar complication of tumor lysis syndrome developed in patient 6, with a huge thymoma of predominantly lymphocytic type during the first cycle.[18]

After CAMP therapy and surgical treatment, mild cardiac dysfunction was observed in two patients (patients 2 and 3[19]) who received whole mediastinal irradiation because of malignant pericardial effusion. No other severe complications were encountered.

DISCUSSION

Complete surgical resection is considered essential in the treatment of thymomas, even for advanced diseases and recurrences.[1–3] Nevertheless, 20 to 40% of patients who undergo surgery for thymoma receive incomplete resection or biopsy alone.[1–3] Moreover, at the initial staging, some lesions are regarded as unresectable; these are usually advanced stage III or stage IV diseases, which are treated with chemotherapy and/or radiotherapy.[6–9]

We originated this aggressive multimodality therapy in February 1988 to improve the survival of patients with advanced or recurrent thymoma. In our study, eligible patients were limited to those with stage III lesions with great vessel invasion, stage IV lesions, or recurrences, because those tumors are not usually manageable by surgery and radiotherapy and are associated with unsatisfactory outcomes.[1–5] Our original chemotherapy regimen for invasive thymoma was designed from single-agent responsiveness for thymoma, which showed that cisplatin, doxorubicin, and corticosteroids had been the most active drugs.[20] Chemotherapy was not only administered in a neoadjuvant setting but also in a postsurgical adjuvant setting, because the initial stagings have not always been accurately estimated, even with CT and magnetic resonance imaging.

Neoadjuvant chemotherapy for invasive thymoma has been attempted in the treatment of locally advanced diseases because of the effectiveness of combination chemotherapy.[10–15] The chemotherapy regimens administered have been diverse, but almost all have included cisplatin and doxorubicin/epirubicin. The reported response rates have been documented to be 69 to 100%, and some patients receiving the treatment have had complete histologic remission. After induction chemotherapy for advanced tumors, the complete resection rates were around 70%. Of patients receiving the multimodality therapy using induction chemotherapy for locally advanced invasive thymoma, 5-year overall survival rates were reported to be between 55 and 95%,[13–15] because the study populations and treatment strategies were different.

In our 14 patients with neoadjuvant therapy, the response rate of CAMP therapy was 92.9%, which was better than or comparable with those of previous reports.[6–15] However, only two patients underwent complete resection, and seven underwent incomplete resection. The other tumors were interpreted as being unresectable after induction chemotherapy. Even after postsurgical radiotherapy, four patients without complete resection remained in PR, and two of them had a short survival. Our low complete resection rate is considered to be a result of the far advancement of the tumors: 13 of 17 patients had stage IV disease and/or recurrent tumors. Furthermore, CT was still incapable of predicting the possibility of performing a radical excision of the tumors after induction chemotherapy.

Patients undergoing incomplete resection or biopsy have been reported to show a significantly shorter survival than those with complete resection.[1–3] Blumberg et al.[2] reported that survival rates in patients with partial resection had been documented at 70 and 28% for 5 and 10 years, and 38 and 24% for biopsy, respectively. All three of our patients who had stage IV disease and were treated with surgery and then adjuvant chemotherapy with or without radiotherapy had distinct residual tumors after the operation. After the adjuvant therapy, two patients had pleural recurrences, but only after disease-free intervals of more than 5 and 2 years, respectively. In the remaining patient, postoperative CAMP therapy

and irradiation have managed the residual disease for more than 10 years. From our available data of those patients with the adjuvant therapy, we think that aggressive postsurgical treatment including chemotherapy is useful to cure or control residual lesions in patients with incomplete resection of the primary tumors, effectively maintaining their quality of life for a longer period.

In the multimodality therapy, some complications were noted. With chemotherapy, fatal infection and tumor lysis syndrome were observed in peculiar patients with parathymic syndrome of hypogammaglobulinemia and extensive lymphocytic thymoma associated with peripheral blood T-cell lymphocytosis,[18] respectively. No mortality was encountered in surgical treatment. After radiation therapy, mild cardiac dysfunction was observed in two patients who had whole mediastinal irradiation for malignant pericardial effusion.[19] This complication is probably caused by doxorubicin and radiation affecting the heart muscle synergistically. On the whole, we think that this multimodality therapy is tolerable as long as attention is paid to any peculiar conditions.

For the recurrent tumors in six patients exhibiting CR, we aggressively performed retreatment. Extrapleural pneumonectomy or partial pleurectomy was carried out in three patients with pleural recurrences, pulmonary metastasectomy was carried out in one patient who was in a postpneumonectomy state, and repetitive radiotherapy was carried out in two patients with mediastinal or diaphragmatic local recurrences. All six patients are still in good general condition 37 to 193 months after the initial treatment. From our experience, we consider that aggressive retreatment for recurrences even after the multimodality therapy is very important for controlling disease and maintaining good quality of life, as previous reports have also advocated.[21,22]

The treatment of advanced thymoma is still controversial. However, investigators have recently advocated the necessity of multimodal approaches to therapy that introduce the enhancement of tumor resectability, cure rate, and/or long-term disease control.[10–15] In studies of such multidisciplinary treatment, Shin et al.[12] and Kim et al.[15] have reported excellent results in the survival of patients with stage III or IV thymoma. Their study protocol was considered a precise long-term treatment, which consisted of induction chemotherapy (cisplatin, doxorubicin, cyclophosphamide, and prednisone), surgical resection, postoperative radiotherapy, and consolidation chemotherapy. From our study, we also recognize the importance of postsurgical adjuvant therapy for patients with advanced disease and/or incomplete resection as well as the importance of retreatment for recurrences after the multimodality therapy. Future studies on the treatment of advanced invasive thymoma should follow a meticulous scheme of a primary multidisciplinary approach to therapy and retreatment of recurrences.

In conclusion, CAMP therapy was highly effective for invasive thymomas. Although this study was limited by its small number of patients and its nonrandomized clinical trial design, we believe that the multimodality therapy containing this chemotherapy is justifiable for the initial treatment of patients with advanced thymoma such as stage III disease with major vessel invasion, stage IV disease, and recurrence. Further studies are warranted to determine the optimal treatment strategy.

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ORIGINAL ARTICLE

Phase II study of weekly chemotherapy with paclitaxel and gemcitabine as second-line treatment for advanced non-small cell lung cancer after treatment with platinum-based chemotherapy

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Abstract
Purpose We evaluated the tolerability and activity of the combination of weekly paclitaxel (PTX) and gemcitabine (GEM) in second-line treatment of advanced non-small cell lung cancer (NSCLC) after treatment with platinum-based chemotherapy.
Patients and methods PTX (100 mg/m^2) and GEM (1,000 mg/m^2) were administered to patients with previous treated NSCLC on days 1 and 8 every 3 weeks.
Results A total of 40 patients (performance status 0/1/2, 7/27/6 pts) were enrolled. The response rate was 32.5% (95% confidence interval: 18.0–47.0%). The median survival time was 41.7 weeks (95% confidence interval: 28.5–54.7 weeks). The median time to disease progression was 19 weeks. Hematological toxicities (grade 3 or 4) observed included neutropenia in 60%, anemia in 15%, and thrombocytopenia in 12.5% of patients. Non-hematological toxicities were mild, with the exception of grade 3 diarrhea, pneumonitis, and rash in one patient each. There were no deaths due to toxicity.
Conclusion The combination of weekly PTX and GEM is a feasible, well-tolerated, and active means of second-line treatment of advanced NSCLC.

Keywords Non-small cell lung cancer · Second-line chemotherapy · Weekly chemotherapy · Gemcitabine · Paclitaxel

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Introduction

The clinical usefulness of second-line chemotherapy has been established for cases of advanced non-small cell lung cancer (NSCLC) in which tumor has recurred or exhibits resistance to treatment after first-line chemotherapy. The effectiveness of docetaxel, pemetrexed, and elrotinib for second-line chemotherapy for NSCLC has been demonstrated in phase III clinical studies [13, 23, 24]. Furthermore, paclitaxel (PTX) and gemcitabine (GEM) have been shown to be effective against NSCLC resistant to platinum preparations [5, 16, 20]. There appears to be partial non-cross-resistance between these drugs and platinum preparations.

In previous attempts at second-line chemotherapy for NSCLC, the response rate was 0–38% for patients treated with PTX alone at intervals of 3 weeks [12, 21, 25] and 8–37.5% for patients treated with low-dose weekly PTX therapy [5, 16, 26, 28]. On the other hand, the rate of response to uncombined GEM therapy was 6–21% [7, 11, 17, 20, 22].

In combined PTX and GEM therapy, the two drugs exhibit interactions with each other but no overlap or synergism of adverse reactions. When this combined

regimen was applied to previously untreated patients with NSCLC, the response rate was high, at 29–46% [1, 3, 4, 8, 15, 18]. When a combination of PTX (administered every 3 weeks) and GEM was used for second-line chemotherapy, the response rate was either 18 or 39% [2, 14].

Weekly chemotherapy for lung cancer has recently been attempted at several facilities [3, 9]. Favorable results of weekly chemotherapy have also been reported for recurrent NSCLC [5, 16, 26, 28]. Compared to standard regimens of chemotherapy, with administration of drugs at intervals of 3–4 weeks, weekly chemotherapy has certain advantages. For example, the single dose level of anti-cancer drugs can be reduced with weekly chemotherapy, and the dose level can be adjusted after the start of treatment depending on signs of hematological toxicity of the drugs or the general condition of individual patients. In comparison with treatment at intervals of 3–4 weeks, weekly chemotherapy was of equal efficacy but had fewer side effects [3]. Weekly chemotherapy is thus a promising means of treating cases of recurrent NSCLC in which bone marrow function has been compromised by first-line chemotherapy.

The present study was undertaken to evaluate the effectiveness and safety of weekly chemotherapy using a combination of PTX and GEM in cases of advanced NSCLC in which tumor had recurred or relapsed after platinum-based first-line chemotherapy or platinum-based first-line chemotherapy had failed to exert efficacy.

Patients and methods

Patient selection

Patients were required to have histologically or cytologically confirmed non-resectable or metastatic NSCLC that had progressed during or after one or more chemotherapy regimens. The trial was initiated after a rest period of at least 4 weeks following previous chemotherapy (2 weeks in the case of radiotherapy). Patients were required to have recovered completely from prior therapy, and to have no ongoing toxicity greater than grade 1. Other eligibility criteria were as follows: measurable lesions; life expectancy of at least 12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; adequate bone marrow reserve (defined as absolute granulocyte count $\geq$ 2,000/ml and platelet count $\geq$ 100,000/ml); adequate hepatic and renal function (defined as serum creatinine level ≤ 2 mg/dl, AST and ALT ≤ 1.5 times the upper limit of normal, and bilirubin ≤ 1.5 mg/dl). Exclusion criteria included pre-existing motor or sensory neurological signs or symptoms $\geq$ grade 2 (Common Terminology Criteria for Adverse Events version 3.0) and active infections. Asymptomatic treated or untreated patients with brain metastases were not excluded from the study. The Ethics Committee of the Tochigi Cancer Center approved the study protocols. Written informed consent was obtained from every patient stating that the patient was aware of the investigational nature of this treatment regimen.

Treatment

Paclitaxel was administered at a dose of 100 mg/m^2 intravenously during a 1-h infusion on days 1 and 8 of the treatment cycle. Gemcitabine was administered at a dose of 1,000 mg/m^2 intravenously during a 30-min infusion on days 1 and 8 of the treatment cycle. Prior to each treatment, patients were given diphenhydramine 50 mg orally, and an H2 blocker intravenously along with dexamethasone 16 mg 30 min before PTX administration. Granisetron 3 mg was administered intravenously as an antiemetic. The length of each chemotherapy cycle was 21 days. Patients who experienced grade 4 leukopenia or neutropenia that lasted for 3 or more days, or who experienced grade 4 thrombocytopenia or reversible grade 2 neurotoxicity or liver dysfunction, received reduced doses of both PTX and GEM (PTX 80 mg/m^2, GEM 800 mg/m^2) for the next cycle. If non-hematological toxicities of grade 3 or higher occurred, treatment was stopped. Subsequent courses of chemotherapy were started after 3 weeks when the leukocyte count was 3,000/mm^3 or more, the neutrophil count was 1,500/mm^3 or more, the platelet count was 75,000/mm^3 or more, serum creatinine were less than 1.5 mg/dl, GOT and GPT were less than twice the upper limit of the normal range, and neurotoxicity was grade 1 or less. If these variables did not return to adequate levels by the first day of the next course of chemotherapy, treatment was withheld until full recovery. If more than 6 weeks passed from the time of the last treatment before these criteria were met or if change in treatment more significant than reduction of dose was indicated, the patient was removed from the study at that time, but still included in the analysis of its results.

Evaluation of responses and toxicity

Pretreatment evaluation included medical history, physical examination, complete blood count, bone marrow examination, serum biochemical analyses,

chest roentgenogram, electrocardiogram, and urinalysis. All patients underwent radionuclide bone scan, magnetic resonance or computerized tomography (CT) of the brain, and CT of the thorax and abdomen. Complete blood count, biochemical tests, serum electrolytes, urinalysis, and chest roentgenograms were obtained before patients received chemotherapy.

Responses and toxicity were evaluated on the basis of tumor images obtained by CT and other techniques, laboratory data, and subjective/objective symptoms and signs before, during, and after administration of the study drugs and during the period from completion of treatment to final analysis. Measurable disease parameters were determined every 4 weeks by various means such as computerized tomography. Evaluation was performed in compliance with the Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines for antitumor activity and with Common Terminology Criteria for Adverse Events version 3.0 for safety. Patients were withdrawn from the study if evidence of tumor progression was obtained. The Institutional Ethical Review Committee gave approval to the study.

The primary endpoint of the study was the response rate. Simon's two-stage optimum design was used to determine sample size and decision criteria. It was assumed that a response rate of 30% among eligible patients would indicate potential usefulness while a rate of 10% would be the lower limit of interest, with $\alpha = 0.05$ and $\beta = 0.10$. Using these design parameters, the fist stage of the study was initially to enroll 18 patients, and this regimen was to be rejected if fewer than two patients had an objective response. If two or more patients responded, accrual was to be continued to 36 patients. Considering the percentage of probable dropout cases, 40 patients were required. Secondary endpoints were toxicity and overall survival. Response and survival rates were both calculated on an intent-to-treat basis. Overall survival and time to progression were measured from the start of this treatment up to the time of death or up to the date of the last follow-up clinical assessment. Survival curves were constructed using the Kaplan–Meier method.

Results

Patient characteristics

Forty patients were enrolled in this study from October 2000 to July 2003. All patients were assessable for toxicity, response, and survival. Characteristics of the 40 patients are listed in Table 1. All 40 patients had received a prior platinum-based chemotherapy regimen (Table 1). Two of these patients had received more than one chemotherapy regimen. All 40 patients were eligible for toxicity assessment. Four patients had received prior chemotherapy in the neoadjuvant setting. Of the 40 patients, 15 had initially responded to platinum-based therapy, 24 patients had achieved stable disease (SD), and one had progressive disease (PD).

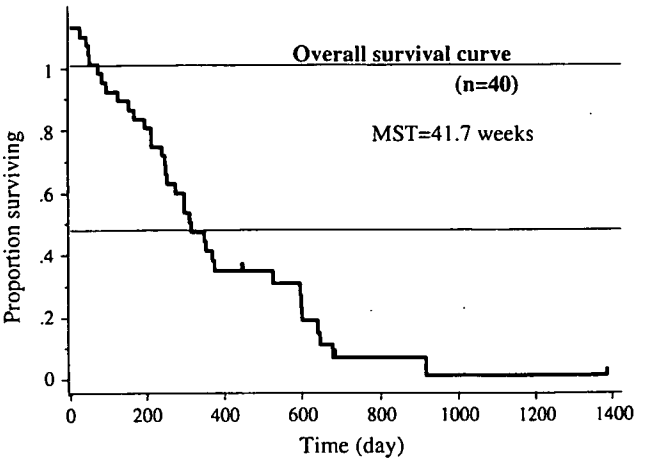

Fig. 1 Kaplan–Meier estimated overall survival curves. Median survival time, 41.7 weeks; 1-year survival rate, 38%

Efficacy of treatment

The mean number of cycles administered per patient was 4, and number of cycles ranged from one to twelve. Three patients required reduction of dose due to neutropenia and thrombocytopenia. Thirteen patients exhibited partial response (PR). Overall response rate was 32.5% (13/40) [95% confidence interval (CI): 18–47%]. SD was achieved in 26 patients (65%), and one (2%) achieved PD. All 40 patients were included in the survival analysis, with a median follow-up time of 82.9 weeks (range 56–263 weeks). The overall median survival time was 41.7 weeks (95% CI: 28.5–54.7 weeks). The 1-year survival rate was 37.5% (15/40) (Fig. 1). The median time to disease progression was 19 weeks.

Toxicities (Table 2)

Table 2 lists toxicities observed during this study. Hematological toxicities included high incidences of leukopenia and neutropenia, with leukopenia and neutropenia of grade 3 or higher occurring in 45 and 60% of patients, respectively. Anemia and thrombocytopenia of grade 3 or higher occurred in 15 and 12.5% of patients, respectively. Non-hematological toxicities

Table 1 Patient characteristics

Eligible patients	40
Gender	
Male	27
Female	13
Age (years)	
Median	59
Range	33–75
Performance status	
0	7
1	27
2	6
Histology	
Adenocarcinoma	30
Squamous cell	8
Large cell	2
Stage III	10
Stage IV	30
Number of metastatic sites	
Median	2
Range	0–3
Location of metastases	
Bone	13
Lung nodules	12
Brain	10
Lymph nodes	7
Liver	5
Adrenals	3
Subcutaneous	1
Prior surgery	4
Prior irradiation	15
Lung only	9
Brain only	4
Lung and bone	2
Prior chemotherapy	40
Cisplatin/vinorelbine	32
Cisplatin/docetaxel	5
Cisplatin/irinotecan	3
Response to prior chemotherapy	
Partial response	15
Stable disease	24
Progressive disease	1

observed included grade 3 pneumonitis in one patient, who exhibited rapid recovery following administration of steroids, grade 3 diarrhea in one, and grade 3 rash in one. Other non-hematological toxicities observed were of grade 2 or less and included nausea in 47.5%, vomiting in 20%, alopecia in 45%, sensory neuropathy in 35%, and fatigue in 32.5% of patients. All of these toxicities disappeared or were improved by symptomatic treatment. There were no deaths due to toxicity.

Discussion

Although a standard regimen of chemotherapy for recurrent NSCLC is being established, it is still important to determine how the outcome of treatment of this cancer can be improved [13, 23, 24]. At this point, the results of large-scale phase III clinical trials indicate single-agent chemotherapy with docetaxel, erlotinib, or pemetrexed as the standard chemotherapy regimen for recurrent NSCLC. In recent years, however, many reports have been published investigating two-drug combined therapy rather than single-agent therapy for recurrent NSCLC, with the objective of further improving therapeutic outcomes [2, 5, 7, 11–14, 20–26, 28].

A large number of reports have been published concerning salvage chemotherapy for recurrent NSCLC. Platinum-based chemotherapy is now used as the first-line chemotherapy at most medical facilities. Reports on second-line chemotherapy for NSCLC published to date have principally concerned uncombined drug therapy or two-drug combined therapy using non-platinum preparations [2, 5, 7, 11, 12, 14, 16, 17, 20–22, 25, 26, 28]. At several facilities, weekly administration chemotherapy has been adopted [5, 16, 26, 28]. Weekly-administration chemotherapy allows single dose levels to be reduced, thus making it possible to adjust the dose levels of anti-cancer agents after the start of treatment depending on adverse reactions or the general condition of individual patients.

Table 3 summarizes the results of two-drug combined therapy for recurrent NSCLC using non-platinum preparations [2, 6, 9, 10, 14, 19, 27]. The studies shown in this table were phase I-II in the case of that reported by Iaffaioli [14], phase III in that by Fossella [9], and phase II in the other studies. The overall response rate varied widely among studies, from 0.8 to 39%. The overall median survival time was 24–47 weeks and the one-year survival rate was 19–46%. Major adverse reactions observed in these studies were signs of hematological toxicity (particularly neutropenia), excluding the studies involving prophylactic G-CSF treatment reported by Androulakis [2] and Wachters [27]. Signs of non-hematological toxicity varied depending on the drugs used, and symptoms and signs unique to each drug were noted.

For combined PTX and GEM therapy for recurrent NSCLC, Androulakis [2] reported an overall response rate of 18%, an overall median survival time of 47 weeks, and a median time to disease progression of 34 weeks. Compared to the present study, the overall response rate reported by Androulakis was lower, while the overall median survival time and median time to disease progression were more favorable in the study by Androulakis. The dosing regimen used by Androulakis involved administration of PTX (175 mg/m^2; day 8), GEM (900 mg/m^2; days 1 and 8), and granulocyte colony-stimulating factor (G-CSF; days

Table 2 Maximum toxicity over 152 cycles (40 patients)

	CTCAE v 3.0 grade (number of patients)					Grade 3 ≤ (%)
	0	1	2	3	4	
Leukopenia	7	4	11	15	3	18 (45)
Neutropenia	6	5	5	17	7	24 (60)
Febrile neutropenia	–	–	–	2	–	2 (5)
Anemia	4	8	22	5	1	6 (15)
Thrombocytopenia	9	21	5	3	2	5 (12.5)
Pneumonitis	36	1	0	1	0	1 (2.5)
Diarrhea	27	9	3	1	0	1 (2.5)
Rash	22	15	2	1	0	1 (2.5)
Nausea	21	19	0	0	0	
Vomiting	32	3	5	0	0	
Fatigue	27	11	2	0	0	
Alopecia	22	17	1	0	0	
Neuropathy-sensory	26	14	0	0	0	
Edema	32	8	0	0	0	
Arthralgia	33	7	0	0	0	

CTCAE v 3.0 Common terminology criteria for adverse events version 3.0

Table 3 Non-platinum regimens used as second-line treatment of non-small cell lung cancer

First author (Ref.)	No. of patients	Regimen and schedule			Response rate (%)	Survival	
						Median (weeks)	1-year (%)
Androulakis [2]	49	P	175 mg/m^2	d 8 q 3w	18	47	37
		G	900 mg/m^2	d 1,8 q 3w			
		G-CSF	150 μg/m^2	d 9–15			
Iaffaioli [14]	37	P	90–240 mg/m^2	d 1 q 3w	39	40	46
		G	1,000 mg/m^2	d 1,8 q 3w			
Fossella [9]	123	FO	2 g/m^2/day	d 1–3 q 3w	0.8	24	19
		V	30 mg/m^2	d 1,8,15 q 3w			
Kosmas [19]	43	D	100 mg/m^2	d 8 q 3w	33	36	28
		G	1,000 mg/m^2	d 1,8 q 3w			
Cao [6]	33	CPT11	300 mg/m^2	d 1 q 4w	9	25	23
		V	30 mg/m^2	d 1,14 q 4w			
Georgoulias [10]	76	CPT11	300 mg/m^2	d 8 q 3w	18.4	38	24.5
		G	1,000 mg/m^2	d 1,8 q 3w			
Wachters [27]	52	CPT11	200 mg/m^2	d 1 q 3w	10	27	30
		D	60 mg/m^2	d 1 q 3w			
		G-CSF	150 μg/m^2	d 2–12			
Present study	40	P	100 mg/m^2	d 1,8 q 3w	32.5	42	38
		G	1,000 mg/m^2	d 1,8 q 3w			

P paclitaxel, *G* gem citabine, *F0* infostamide, *V* vinorebine, *D* docetaxel, *CPT-11* irinotecan, *G-CSF* granulocyte colony-stimurating factor, *d* day, *q* every

9–15), with each cycle of treatment lasting for 3 weeks. Because their regimen involved prophylactic administration of G-CSF, the incidence of grade 3 or worse neutropenia was lower than that in the present study (12 vs. 60%). However, the incidence of grade 2 or worse fatigue (a sign of non-hematological toxicity) was lower in the present study (4%) than in that reported by Androulakis (51%).

Belani [19] reported the results obtained with combined use of PTX and GEM as first-line chemotherapy for NSCLC. In their study, PTX was administered using two regimens and a comparison was made between treatment with PTX on day 1 (200 mg/m^2) and weekly treatment with PTX on days 1 and 8 (100 mg/m^2/dose; identical to the regimen used in the present study). According to their report, the response rate was 45% for the first regimen and 46% for the second regimen, the median survival time was 42 and 39 weeks and the 1-year survival rate 46 and 41% for the first and second regimens, respectively. Efficacy thus did not differ

significantly between the two regimens. Signs of hematological toxicity were the major adverse reactions observed following treatment with both regimens. The incidences of neutropenia and alopecia were lower with the weekly regimen. On the basis of these results, Belani concluded that weekly PTX treatment combined with GEM is also useful as first-line chemotherapy for NSCLC.

In conclusion, weekly chemotherapy with PTX and GEM is a tolerable and active regimen for patients with advanced NSCLC previously treated with platinum-containing chemotherapy regimens. It should be recommended as a candidate regimen in planning a phase III clinical study of NSCLC previously treated with platinum-containing chemotherapy, and will ultimately be evaluated in a phase III clinical study.

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P04-3-5 Cytotoxic Chemotherapy II, Tue, 16:00 - 17:30

Phase I/II study of oral TS-1 and gemcitabine in elderly patients with advanced non-small-cell-lung cancer (NSCLC): Thoracic Oncology Research Group Study 0502

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Background: Optimal treatment for elderly patients with NSCLC has been under active investigation. This study evaluated the safety and initial efficacy of a novel combination regimen of oral fluoropyrimidine TS-1 plus gemcitabine (GEM) for elderly patients (pts) with advanced NSCLC.

Methods: A phase I/II trial in 11 centers examined TS-1 and GEM in pts with age ≥ 70, stage IIIB/IV previously untreated NSCLC. The starting dose was 60 mg/day (day 1-14) for TS-1 and 800 mg/m^2 for GEM (day 8, 15). GEM was increased to 1000 mg/m^2 at dose level 2 and TS-1 was increased to 80 mg/day at dose level 3. Phase II portion of the study assessed the efficacy and tolerability of the combination regimen at the dose determined in the phase I portion. The primary endpoint was objective response rate.

Results: Twenty two pts were enrolled in the phase I portion: 6 pts on dose level 1, 10 on dose level 2 and 6 on dose level 3. Median age of this group was 75 yrs (range 70-85). Dose limiting toxicities included Gr. 4 neutropenia (2 pts) and Gr.3 skin toxicity (4 pts). The recommended dose (RD) was TS-1 60 mg/day and GEM 1000 mg/m^2, with which 20 pts were subsequently treated in the phase II portion. The median age of 30 pts treated with the RD was 76 yrs (range 70-85). Grade (Gr) 3/4 toxicities include neutropenia (12 pts; 7 with Gr 4), thrombocytopenia (4 pts; 0 with Gr 4), skin toxicity (8 pts), thrombus (1 pt) and peumonitis (2 pts). Nine patients (30%, 95% confidence interval [CI] = 14 to 46%) had partial responses and 16 (53%, 95% CI = 35 to 71%) had stable disease.

Conclusion: Encouraging antitumor activity and safety of TS-1 plus gemcitabine support further development of this combination therapy for elderly patients with advanced NSCLC.

Phase II Study of Paclitaxel and Irinotecan Chemotherapy in Patients With Advanced Nonsmall Cell Lung Cancer

Fumihiro Oshita, MD, Haruhiro Saito, MD, Kouzo Yamada, MD, and Kazumasa Noda, MD

Objectives: We conducted a phase II study of combination chemotherapy with paclitaxel (Pac) and irinotecan (CPT) to determine the qualitative and quantitative toxicities and efficacy of the combination against advanced nonsmall cell lung cancer (NSCLC).

Patients and Methods: 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.

Results: Between May 2002 and July 2004, 39 of registered 46 patients received 4 to 6 cycles of chemotherapy, and 7 patients discontinued treatment because of disease progression in 5 patients and grade 2 pneumonitis in 2 patients. Grade 3 anemia, leukopenia, neutropenia, and elevation of bilirubin occurred in 4.0%, 0.5%, 1.0%, and 0.5%, respectively. Twenty-one patients responded, and the overall response rate was 45.6%. The median survival time was 355 days and the 1-year survival rate was 47.8%.

Conclusion: Pac plus CPT was efficacious and safe in NSCLC.

Key Words: paclitaxel, irinotecan, nonsmall cell, lung cancer

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Current chemotherapy regimens for metastatic nonsmall cell lung cancer (NSCLC) are not particularly effective, and the disease cannot be cured even with the most effective chemotherapy. Current international guidelines recommend the use of platinum-based chemotherapy for patients with advanced NSCLC,[1] and the use of doublets including platinum plus a third-generation agent has been widely accepted for patients with a good performance status. A meta-analysis of the published literature clearly showed the superiority of platinum-containing regimens in terms of objective response rate, and this superiority was found throughout the subgroup analyses performed.[2] The study results also confirmed that platinum-based therapy is generally associated with higher toxicity, particularly nausea and vomiting, hematologic toxicity, and nephrotoxicity. Nevertheless, platinum-based regimens can be administered as safely as nonplatinum therapies when patients are selected correctly. However, this study did not include every combination of nonplatinum drugs, and it is necessary to examine every such new combination for efficacy and toxicity.

Combined analysis of two randomized phase III studies demonstrated that irinotecan (CPT) combined with cisplatin significantly improves survival compared with vindesine and cisplatin in patients with advanced NSCLC.[3] In Japan, CPT is considered a key drug against NSCLC. Preclinical studies that have evaluated combinations of a camptothecin with a taxane have yielded promising results, and several studies have demonstrated an additive or synergistic interaction between camptothecin and taxanes.[4] Our previous phase I study of a Pac and CPT combination showed that pneumonitis was the dose-limiting toxicity and led to a recommendation of Pac 160 mg/m^2 and CPT 60 mg/m^2 every 2 weeks for further study.[5] This study also demonstrated an objective response rate of 58.3% and a 1-year survival rate of 54.2%. Accordingly, we expected the combination of Pac and CPT to display high activity against NSCLC and designed a phase II study to determine the efficacy and toxicities.

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, an expected survival of at least 12 weeks, age <70 years, Eastern Cooperative Oncology Group PS score ≤1, leukocyte count ≥4000/μL, hemoglobin ≥10 g/dL, platelet count ≥100,000/μL, total serum bilirubin ≤1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase ≤90 IU/L, and serum creatinine ≤1.5 mg/dL. Patients who had experienced postoperative recurrence were eligible for this study, but a 4 or more week rest period was required after surgery. 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 4 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

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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 $\mu g/m^2$ per day or 2 $\mu g/kg$ per day, was administered subcutaneously on days 6 to 10. Patients were given a 5-HT_3 antagonist intravenously. Subsequent courses of chemotherapy were started when patients satisfied the organ function criteria: leukocyte count $\geq 3000/\mu L$, neutrophil count $\geq 1500/\mu L$, platelet count $\geq 75{,}000/\mu L$, and less than grade 1 nonhematologic toxicities, except alopecia. Grade 3 nausea and vomiting did not preclude subsequent courses of chemotherapy. Chemotherapy was repeated for a maximum of 6 courses unless the disease progressed, but it was stopped if the tumor response was judged to be NC after 4 courses. Tumor response was evaluated according to RECIST criteria.[6] Toxicities were evaluated according to the NCI-CTC (version 2) criteria.[7]

Study Design

We chose a 50% response rate as a desirable target level and a 30% response rate as uninteresting. The study design had power in excess of 90% and less than 10% error; therefore, 22 assessable patients in the first step and 24 in the second step were required according to the optimal design of Simon.[8] We decided to stop the study if there were fewer than 8 responders in the first step. The regimen was defined as active if there were 18 or more responders out of the total of 46 patients. Overall survival was estimated by the method of Kaplan and Meier.

RESULTS

Between May 2002 and July 2004, 46 patients were registered in the phase II study (Table 1). A total of 22 patients were registered for assessment of response in the first stage. Nine of 22 patients in the first stage responded and 24 patients were registered in the second stage. A total of 198 cycles was administered to 46 patients. Thirty-nine patients received 4 to 6 cycles of chemotherapy, except for 7 patients who discontinued treatment in the first or second cycles because of disease progression in 5 patients and grade 2 pneumonitis with pulmonary infiltration in 2 patients. Adverse effects and events are summarized in Table 2. Grade 3 anemia, leukopenia, neutropenia, and elevation of bilirubin occurred in 4.0%, 0.5%, 1.0%, and 0.5%, respectively. There were no grade 4 toxicities.

Twenty-one of 46 patients achieved partial response, 18 no change, 6 progressive disease, and 1 not evaluated, and the overall response rate was 45.6% in phase II study. The median duration of partial response was 154 days (range, 76–380 days). The median survival time was 355 days and the 1-year survival rate was 47.8% (Table 3). The outcome in 70 patients including those from the phase I study (5) demonstrated that 1 patient achieved complete response, 34 PR, and the overall response rate was 50.0%. The median survival time was 361 days and the 1-year survival rate was 50.0%.

TABLE 1. Patient Characteristics

Characteristic	Value
Total	46
Age (years)	
Median	61
Range	43–69
Gender (no. patients)	
Male	29
Female	17
Performance status (ECOG) (no. patients)	
0	12
1	34
Clinical stage (no. patients)	
IIIB	6
IV	34
Postoperative recurrence	6
Histology (no. patients)	
Adenocarcinoma	36
Others	10
No. metastatic organs (no. patients)	
1	27
≥2	13
Brain metastasis (no. patients)	8

TABLE 2. Adverse Effects and Events

	NCI-CTC Grade (No. Cycles)					
Toxicity	0	1	2	3	4	% ≥Grade 3
Hemoglobin	29	137	24	8	0	4.0
Leukocyte	162	23	12	1	0	0.5
Neutrophil	167	19	10	2	0	1.0
Platelets	188	10	0	0	0	—
Bilirubin	165	22	10	1	0	0.5
Creatinine	192	6	0	0	0	—
SGOT	146	51	1	0	0	—
SGPT	135	55	8	0	0	—
Infection	194	3	1	0	0	—
Nausea/vomiting	143	51	4	0	0	—
Diarrhea	165	31	2	0	0	—
Myalgia	97	76	25	0	0	—
Arthralgia	110	64	24	0	0	—
Neuropathy	107	76	15	0	0	—
Fever	183	14	1	0	0	—
Allergic reaction	195	3	0	0	0	—
Alopecia	95	79	24	0	0	—
Pneumonitis	196	0	2	0	0	—
Hypotension	193	5	0	0	0	—
Arrhythmia	194	4	0	0	0	—

NCI-CTC, National Cancer Institute-Common Toxicity Criteria (version 2).

DISCUSSION

The objective response rate of 50.0% and 1-year survival rate of 50.0% with our nonplatinum Pac and CPT regimen in 70 patients in phase I and phase II studies are somewhat better than in a large phase III trial of 4 platinum-based chemotherapy regimens, which showed response rates of 17% to 22% and 1-year survival rates of 31% to 34%.[9] The

TABLE 3. Therapeutic Outcome in Phase II Study

Response	No. Patients
Complete response	0
Partial response	21
No change	18
Progressive disease	6
Not evaluated	1
Response rate (%)	45.6
Median survival time (days)	355
% of 1-year survivor	47.8

antitumor activity of the Pac and CPT combination is thought to be attributable to a synergistic action between these drugs. A possible mechanism of the synergy is a drug-drug interaction, such as that shown in a pharmacokinetic study that demonstrated elevation of the AUC of CPT and SN-38 by Pac infusion.[10] Although we acknowledge the possibility that Pac and CPT might affect each other's pharmacokinetics, increasing their activity against NSCLC, we also considered that another possible mechanism for this high activity of the Pac and CPT combination might be related to influx and efflux in the cell system. The combination of Pac and SN-38 downregulates the level of multidrug resistance-associated protein, which may be an efflux pump for cisplatin, in ovarian cancer cell lines, suggesting that this combination will overcome drug resistance.[11]

The combination of Pac and CPT also appears useful in that little toxicity was observed in this study. No patients experienced grade 4 toxicities. All patients, except the 5 patients who developed disease progression during treatment and the 2 patients who experienced grade 2 pneumonitis with pulmonary infiltration, were able to receive 4 to 6 cycles of this therapy. The pneumonitis was thought to be attributable to a booster effect of an allergic reaction when 180 mg/m^2 or higher of Pac was combined with CPT in the phase I study, but no patients experienced pneumonitis during cycles 2 to 6 of chemotherapy in this phase II study. Therefore, pneumonitis was seen at a frequency similar to that in other combination chemotherapies. Neutropenia was mild because of the prophylactic use of G-CSF in this study. We used G-CSF when monocytopenia less than 150/μL appeared in the phase I study,[5] and most patients received G-CSF for 5 days starting on days 5, 6, or 7. Consequently, G-CSF was given routinely for 5 days from day 5 to day 9 in every cycle in the present study. This less toxic regimen may be helpful in the treatment of high-risk patients, such as the elderly or those with poor performance status or moderately severe complications.

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Prospective Validation for Prediction of Gefitinib Sensitivity by Epidermal Growth Factor Receptor Gene Mutation in Patients with Non-Small Cell Lung Cancer

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Introduction: We evaluated the efficacy of gefitinib monotherapy prospectively in patients with advanced or pretreated non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations.

Methods: Patients with NSCLC were examined for EGFR exon 19 deletion mutations by fragment analysis and for EGFR L858R point mutations by the Cycleave polymerase chain reaction technique. EGFR mutation-positive patients with locally advanced, metastatic, or recurrent/refractory NSCLC that was not curable with surgery or thoracic radiotherapy were candidates for gefitinib treatment administered at 250 mg/day until disease progression.

Results: Mutations of the EGFR gene were detected in 27 (41%) of 66 patients. Ten had exon 19 deletion, and 17 had L858R. Twenty-one patients harboring EGFR mutations were treated with gefitinib and were considered assessable for responses and adverse events. Nineteen patients with EGFR mutations achieved objective responses (three complete responses and 16 partial responses), resulting in an overall response rate of 90.5% (95% confidence interval, 69.6%–98.8%). The median progression-free survival was 7.7 months (95% confidence interval, 6.0 mo to not reached). The median overall survival has not been reached. Common adverse events were skin toxicity, diarrhea, and elevated aminotransferases, but no pulmonary toxicity was observed.

Conclusions: Detection of common EGFR mutations seems to be useful for selecting patients with NSCLC who would likely benefit from gefitinib monotherapy.

Key Words: EGFR, Gefitinib, Lung cancer, Mutations, Drug sensitivity.

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Lung cancer remains the most common cause of cancer death in both men and women worldwide. Lung cancer frequently presents at an advanced and biologically aggressive stage, resulting in poor prognosis. Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers. Currently, platinum-based combination chemotherapy regimens, including several active new chemotherapeutic agents, comprise the standard option for patients with advanced NSCLC. However, various combinations of drugs have similar efficacy, producing objective response rates of 30 to 40%, median survival time of eight to 10 months, and 1-year survival rates of 30 to 40%.[1,2] These results remain unsatisfactory, and new modalities of treatment are urgently awaited. Recently, novel molecular targeted strategies that block cancer progression pathways have been suggested as the ideal treatment to control cancer and are considered an exciting therapeutic approach for treating NSCLC.[3]

The epidermal growth factor receptor (EGFR) is a 170 kDa receptor tyrosine kinase and a member of the erbB receptor family that plays a pivotal role in the signaling processes of tumor progression.[4–6] EGFR is overexpressed in several solid tumors, including NSCLC, and it is one of the leading therapeutic molecular targets.[7] Gefitinib is an orally bioavailable, selective EGFR tyrosine kinase inhibitor (TKI) and was the first targeted drug for NSCLC. Phase II and III monotherapy trials for patients pretreated for NSCLC demonstrated objective response rates of only 8 to 18%.[8–10] However, subset analyses of these trials and a retrospective study[11] showed a small group of clinical responders comprising women, patients with adenocarcinomas, nonsmokers, and Japanese or Asian patients. These results suggest that identifying predictive molecular or genetic biomarkers for gefitinib sensitivity may be useful for selecting patients who are most likely to benefit from treatment.

In 2004, three independent groups reported that somatic EGFR mutations correlated with sensitivity of NSCLC to gefitinib or erlotinib, another EGFR TKI.[12–14] Subsequently, several groups confirmed this striking correlation between EGFR mutations and gefitinib sensitivity, yielding a response rate of about 60 to 94% in retrospective analyses.[15–22] EGFR mutations are likely to be significantly associated with survival benefit attributed to gefitinib treatment.[17,18,21] In con-

trast to these results, recent reports concerning molecular analyses of large-scale phase II and III trials showed lower response rates than previously reported and no survival benefit in patients with mutations treated with TKIs.[23–26] Around the same time, the EGFR gene amplification/copy number was demonstrated as another useful predictive molecular marker of TKI efficacy.[23,26–28] However, these contradictory results were obtained through the retrospective collection of tumor samples, and prospective validation studies that predict TKI efficacy by EGFR mutations are needed.

Data from previous reports show that in-frame deletions in exon 19 and specific missense mutation of codon 858 in exon 21 (L858R) account for about 90% of all EGFR mutations, and about 80% of responders to gefitinib or erlotinib harbor either of these two hotspot mutations. Therefore, we developed a rapid, sensitive screening assay of two hotspot mutations[29] and conducted a prospective cohort study to explore the prediction of gefitinib sensitivity in EGFR mutation-positive patients.

MATERIALS AND METHODS

Study Design

This prospective cohort study was conducted to identify patients with NSCLC who would most likely benefit from gefitinib treatment according to their EGFR mutation. Patients with EGFR mutation were treated with oral administration of gefitinib at a dose of 250 mg once a day until disease progression or intolerable toxicity occurred, or until the patient refused to continue treatment. The primary endpoint was objective tumor response rate. Secondary endpoints included adverse effects, disease control rate (response + stable disease), progression-free survival (PFS), and overall survival (OS). This study was approved by the institutional review board of Aichi Cancer Center Hospital.

Patient Eligibility

Eligibility criteria for gefitinib treatment were adult (age ≥20 yr) with cytologic or histologic confirmation; locally advanced, metastatic, or recurrent/refractory NSCLC that was not curable by surgery or radiotherapy; harboring EGFR mutation; and one or more measurable or assessable lesions. All patients were admitted to the study regardless of prior treatment, extent of performance status (PS), or main organ functions. The exclusion criteria were pulmonary fibrosis, interstitial pneumonia, or prior treatment with an EGFR TKI or antibody. All patients gave written informed consent in accordance with institutional regulations before entering the study.

Efficacy and Toxicity Evaluation

Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors[30] and were confirmed by repeated imaging studies after 4 to 8 weeks of gefitinib treatment. During the treatment and for 30 days after the last dose of gefitinib, patients were monitored for adverse events, which were graded using Common Terminology Criteria for Adverse Events, version 3.0. PFS was assessed from the date of gefitinib treatment until the date of objective disease progression, death from any cause, or the last follow-up. OS was assessed from the date of gefitinib treatment until the date of death from any cause, or the last follow-up.

Detection of EGFR Mutations

Genomic DNA was extracted from tumors embedded in paraffin blocks or from aspirated tumors obtained in pleural effusions, superficial lymph nodes, or subcutaneous metastasis. All specimens were reviewed by a single reference pathologist (Y.Y.) and marked grossly near the tumor-rich lesion on an unstained slide to enrich the tumor cell population as much as possible.

We performed mutational analyses of exon 19 deletion and the L858R point mutation of the EGFR gene, as previously described.[29] Briefly, exon 19 deletion was determined by common fragment analysis using polymerase chain reaction (PCR) with an FAM-labeled primer set, and the PCR products were electrophoresed on an ABI PRISM 310 (Applied Biosystems, Foster City, CA). The shorter segment of DNA amplified by PCR showed a deletion mutation in a new peak in an electropherogram. The L858R mutation was detected by the Cycleave real-time quantitative PCR technique using the Cycleave PCR core kit (Takara Co. Ltd., Ohtsu, Japan) with an L858R-specific cycling probe and a wild-type probe. Fluorescence intensity was measured with a Smart Cycler system (SC-100, Cepheid, Sunnyvale, CA).

Statistical Analysis

Data were analyzed using the chi-square test; $p < 0.05$ was regarded as significant. Confidence intervals (CI) were calculated using binomial CIs. PFS and OS were calculated using the Kaplan–Meier method and compared between two EGFR mutation groups using log-rank test. All the analyses were performed with Stata 8.2 for Macintosh (Stata Corp, College Station, TX).

RESULTS

Sampling Procedure for Detecting EGFR Mutations

Sixty-six consecutive patients with NSCLC were examined to detect the EGFR mutations from November 2004 through August 2005 at Aichi Cancer Center Hospital. Of these patients' samples, 23 specimens were obtained from bronchoscopic biopsy, 22 from computed tomography/ultrasound-guided needle biopsy, 13 from percutaneous aspiration (seven from pleural effusion, four from lymph nodes, and two from skin metastases), two from biopsy (one from tonsil metastasis and one from skin metastasis), and six from surgery with general anesthesia (three from thoracotomy, two from thoracoscopy, and one from mediastinoscopy (Table 1). Sixty samples (91%) were obtained from the biopsy or aspiration method. Tumor tissues or aspirates were procured at the time of initial diagnosis in 52 patients and at the time of tumor progression in 14 patients.

Patient Characteristics and EGFR Mutations

Mutations of the EGFR gene were detected in 27 (41%) of 66 patients. Ten of these had the deletion in exon 19, and

TABLE 1. Patient Characteristics and Sample Procurement According to EGFR Mutation Status

	EGFR Mutation Status			
	All	Mutation	Wild type	p
All cases	66	27 (21)	39	
Sex				0.175
Male	36	10 (8)	26	
Female	30	17 (13)	13	
Age (yr)				0.5084
≤64	31	14 (11)	17	
>64	35	13 (10)	22	
Histology				0.0199
Adenocarcinoma[a]	59	27 (21)	32	p ([a] vs. [b])
Squamous cell[b]	2	0	2	
Large cell[b]	2	0	2	
Pleomorphic[b]	1	0	1	
NSCLC NOS[b]	2	0	2	
Smoking status				0.0002
Never smoker[c]	24	17 (13)	7	p ([c] vs. [d])
Former smoker[d]	17	9 (7)	8	
Current smoker[d]	25	1 (1)	24	
Stage at initial diagnosis				0.6348
IA[e]	2	1	1	p ([e] vs. [f])
IIB[e]	4	2 (2)	2	
IIIA[f]	3	0	3	
IIIB[f]	16	3 (2)	13	
IV[f]	41	21 (17)	20	
Performance status				0.6059
0/1	51	20 (14)	31	p (0/1 vs. ≥2)
2	7	3 (3)	4	
3	3	1 (1)	2	
4	5	3 (3)	2	
Prior first treatment				ND
No	8	5 (5)	3	
Surgery	3	3 (1)	0	
Thoracic irradiation	4	2 (2)	2	
Chemoradiotherapy	10	2 (1)	8	
Bone irradiation	6	3 (3)	3	
Brain irradiation	6	3 (2)	3	
Sclerotherapy for effusion	1	1 (1)	0	
Chemotherapy	28	8 (6)	20	
Prior chemotherapy				0.4337
0	28	13 (12)	15	p (0 vs. ≥1)
One regimen	28	10 (6)	18	
Two regimens	8	4 (3)	4	
Three regimens	2	0	2	
Method for sample procurement				ND
Bronchoscopic biopsy	23	11	12	
CT/US-guided needle biopsy	22	6	16	
Pleural effusion aspiration	7	4	3	
LN/skin aspiration	6	2	4	
Tonsil/skin biopsy	2	0	2	
Thoracotomy	3	2	1	
VATS	2	1	1	
Mediastinoscopy	1	1	0	

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; NOS, not otherwise specified; ND, not done; CT/US, computed tomography/ultrasound; LN, lymph node; VATS, video-assisted thoracoscopy. Superscript letters indicate groups compared in the statistical analysis. Numbers in parentheses represent the numbers of patients receiving gefitinib treatment.

17 were the point mutation at codon 858. As previously reported,[12–14,17] the EGFR mutations were significantly associated with adenocarcinoma histology and never-smoking status (Table 1). However, the EGFR mutation status was not significantly correlated with sex, age, PS, stage at initial diagnosis, or prior chemotherapy. Twelve patients received gefitinib treatment as the first-line chemotherapy; five patients desired first-line gefitinib therapy, and the other seven were unfit for conventional chemotherapy because of age (one patient, age 84 yr), cardiac disease (one patient), widespread bone metastases (two patients), and poor PS (3–4 in three patients).

Clinical Response and Survival

Of 27 patients harboring EGFR mutation, 21 were treated with gefitinib and were assessable for objective responses (Table 2) and adverse events (Table 3). The median interval of gefitinib treatment was 5.9 months (range, 0.67 to 11.4 mo). Of the assessable 21 patients, 19 patients achieved objective responses (three complete response and 16 partial response), for an overall response rate of 90.5% (95% CI, 69.6–98.8%). One patient had stable disease, giving an overall disease control rate of 95.2% (95% CI, 76.2–99.9%). According to EGFR mutation classes and PS, the objective responses were seven of eight for the exon 19 deletion, 12 of 13 for the L858R point mutation, 13 of 14 in PS 0 to PS 1 patients, and 6 of seven in PS 2 to PS 4 patients. The response to gefitinib did not differ significantly according to the mutation class or PS.

The median PFS was 7.7 months (95% CI, 6.0 mo to not reached) (Figure 1A). The median OS has not been reached at present (Figure 1B). Subset analyses showed that PFS was greater in patients with the exon 19 deletion than in those with the L858R point mutation (log rank test, $p = 0.04$; Fig 2*A*). The median PFS for the exon 19 deletion group was 7.8 months (95% CI, 7.6 mo to not reached); for the L858R mutation group, median PFS was 6.0 months (95% CI, 2.6 to 7.7 mo). OS did not differ significantly between the two types of mutations (Figure 2B). No difference was observed in PFS and OS between never-smokers and current/former smokers (data not shown).

TABLE 2. Response of EGFR Mutation-Positive Patients to Gefitinib Treatment

	EGFR Mutation Status		
	Exon 19 Deletion ($n = 8$)	L858R Mutation ($n = 13$)	Total ($n = 21$)
CR	1 (12.5%)	2 (15.4%)	3 (14.3%)
PR	6 (75%)	10 (76.9%)	16 (76.2%)
Overall response rate (CR + PR)	7 (87.5%)	12 (92.3%)	19 (90.5%)
SD	1 (12.5%)	0	1 (4.8%)
Disease control (CR + PR + SD)	8 (100%)	12 (92.3%)	20 (95.2%)
Progressive disease	0	1 (7.7%)	1 (4.8%)

EGFR, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease.

TABLE 3. Number (%) of Patients with Treatment-Related Adverse Events ($n = 21$)

	Grade				
	0	1	2	3	4
Skin toxicity	15 (71)	4 (19)	2 (10)	0	0
Diarrhea	13 (62)	3 (14)	3 (14)	2 (10)	0
Elevated aspartate aminotransferase/ alanine aminotransferase	15 (71)	1 (5)	2 (10)	3 (14)	0
Nail changes	17 (81)	3 (14)	1 (5)	0	0
Mucositis	20 (95)	1 (5)	0	0	0
Joint pain	20 (95)	1 (5)	0	0	0

Adverse Events

All 21 patients were evaluated for drug-related adverse events. The most common adverse events were skin toxicity, diarrhea, and elevated asparatate aminotransferase/alanine aminotransferase (AST/ALT) (Table 3). The grade 3 adverse events of diarrhea and elevated AST/ALT occurred in two (10%) and three (14%) patients, respectively. These events occurred slightly more frequently than in previous studies.[8,9] No grade 4 adverse events or pulmonary toxicity were observed. Seven patients required an interruption of treatment, lasting 2 to 4 weeks, because of grade 2/3 diarrhea or grade 3 elevated transaminases. Two patients withdrew: one after 3 weeks of gefitinib treatment because of grade 3 diarrhea, and the other after 9 weeks of gefitinib treatment because of grade 2 nail changes.

DISCUSSION

In the present study, we have observed that the objective response rate in our patients was similar to that in previous reports. We also found that PFS and OS seem promising in identifying gefitinib-sensitive patients regardless of whether the study includes patients unsuited for conventional cytotoxic chemotherapy because of age, cardiac disease, widespread bone metastases, or poor PS (3 to 4). Our favorable data might have resulted because we selected patients harboring one of two hotspot mutations (exon 19 deletion and exon 21 L858R mutation). Greulich et al.[31] examined NIH-3T3 cells transformed with various EGFR mutants and showed that a distinct EGFR mutation confers differential sensitivity to TKIs. They demonstrated greater sensitivity to TKIs in cell lines with the two hotspot mutations than with the G719S mutation, and insensitivity to TKIs in cell lines with exon 20 insertion (D770-N771 ins) mutation. These in vitro data may explain, at least partially, our promising results for detecting these two sensitive mutations.

We previously reported that patients with the EGFR exon 19 deletion respond significantly better to gefitinib than those with the L858R mutation ($p = 0.0108$).[17] Our current data show no difference in gefitinib sensitivity and OS after

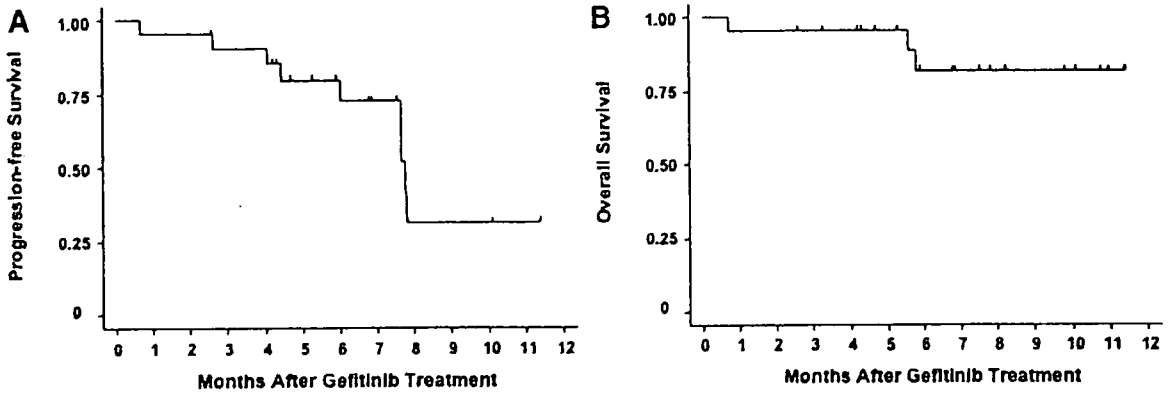

FIGURE 1. Kaplan–Meier estimates of (*A*) progression-free survival and (*B*) overall survival for patients with EGFR mutations (n = 21). The median progression-free survival was 7.7 months (95% CI, 6.0 mo to not reached). The median survival was not reached.

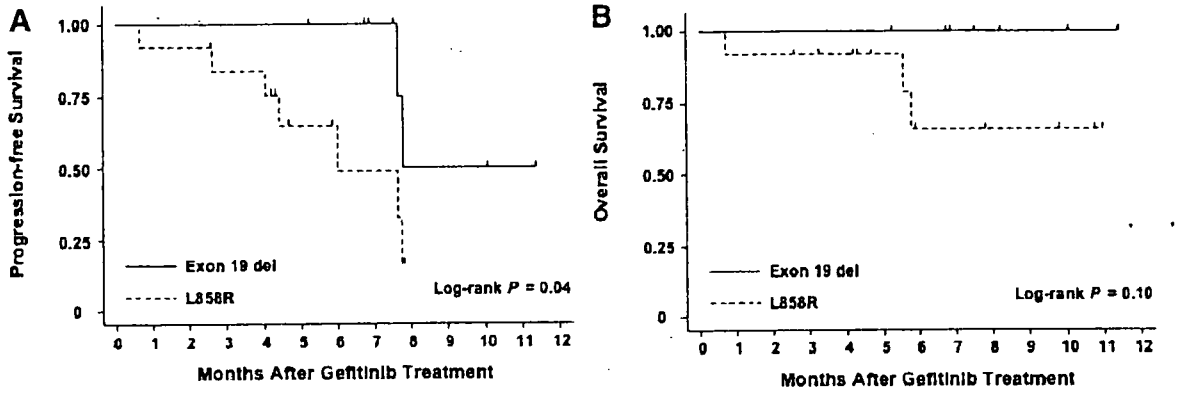

FIGURE 2. Kaplan–Meier estimates of (*A*) progression-free survival and (*B*) overall survival for patients with EGFR mutations according to the exon 19 deletion (n = 8) and L858R mutation (n = 13). The median PFS for the exon 19 deletion group was 7.8 months (95% CI, 7.6 mo to not reached); for the L858R mutation group, median PFS was 6.0 months (95% CI, 2.6 to 7.7 mo).

gefitinib treatment between these two groups of patients, although we observed a greater PFS in the EGFR exon 19 deletion group than in the L858R group. It is possible that the number of patients (eight with exon 19 deletion and 13 with L858R) was too small to detect a statistically significant difference in OS. Riely et al.[32] reported recently that patients with exon 19 deletion have a significantly longer survival after TKI treatment than those with the L858R mutation (p = 0.01). These findings suggest that the EGFR exon 19 deletion might be a better predictor of the efficacy of TKIs than the L858R mutation.

EGFR mutations are significantly associated with patients with adenocarcinomas, patients of Asian origin, females, and patients who had never smoked—clinical factors also associated with patients who respond to gefitinib.[13,14,24,33] A phase II trial using gefitinib monotherapy as the first-line therapy for patients with adenocarcinoma histology and never-smoking status was recently completed in South Korea and reported promising data (e.g., an objective response rate of 69% and estimated 1-year survival rate of 73%).[34] However, this trial did not select patients using biomarkers, and we believe the benefit of gefitinib therapy could be enhanced by selecting individual patients according to appropriate biomarkers. Very recently, two prospective phase II studies that had selected patients based on molecular biomarkers demonstrated that EGFR mutations[35] and gene copy number assessed by fluorescence in situ hybridization (FISH)[36] can predict clinical outcomes in TKI-treated NSCLC patients.

The grade 3 adverse events of diarrhea and elevated AST/ALT were observed in five patients (24%); this is a higher rate than that reported in two previous phase II studies that reported rates of adverse events of 1.5%[8] and 7%[9] at a gefitinib dose of 250 mg per day. The reasons for our higher rate of adverse events are unknown. Although adverse events related to gefitinib treatment are generally thought to be mild and tolerable, they should not be discounted.

Most studies have detected EGFR mutations using direct sequencing or single-strand conformation polymorphism analysis for exons 18 to 21.[37] These techniques are less sensitive when applied to a small amount of tumor cells from the biopsy or aspiration samples.[38] We were able to detect