taxane failure, and it has shown a survival benefit in comparison with placebo in unselected non-small cell cancer(21). By contrast, it was impossible to show any overall survival benefit of gefitinib in a group of similar cases that were almost the same although the results were marginal(22,23), and while significant prolongation of survival time was observed in Asians (no Japanese were included) by post-study stratification, no difference in survival time at all from the placebo control group was observed in Caucasians. Moreover, four trials of standard chemotherapy (carboplatin+paclitaxel, gemcitabine+cisplatin) ±EGFR-TKI all yielded negative data(17～20), and in a comparative study with gefitinib as intensification chemotherapy for stage III non-small cell cancer the survival time of the gefitinib group was instead significantly poorer than in the control group(24). Adjuvant studies using EGFR-TKIs in resected cases was started in Japan and North America but case entry was poor, and it was stopped before completion(25).

Two comparative studies of docetaxel versus the EGFR-TKI gefitinib in cases in which platinum-taxane was ineffective yielded different results. Even though the response rate to gefitinib by the Japanese patients was higher than in the Western population, it was impossible to demonstrate non-inferiority versus docetaxel in the V15-32 study conducted in Japan(26). By contrast, non-inferiority was demonstrated in the Interest study conducted in a large number of cases in Western countries(27).

The majority of the results of these studies were not what the investigators expected (Table 2), and numerous questions have arisen.

1) In placebo-controlled studies in cases in which platinum-taxane therapy was ineffective, the ISEL study (gefitinib) was negative(22), whereas BR-21 (erlotinib) was positive(21). The efficacy of gefitinib was marginal, but no difference at all was observed in the Western subjects. Differences in dosage were stated as the reason, but that is not a satisfactory explanation.

2) Does not the fact that Intact I & II (gefitinib)(17,18) and Talent(19) & Tribute (erlotinib)(20) were all negative studies conflict with the evidence in BR-21 study. There is the explanation based on their effects on the cell cycle that anti-cancer drugs and EGFR-TKIs act antagonistically when administered simultaneously.

3) Non-inferiority versus docetaxel was demonstrated in the Interest study (gefitinib) even though the ISEL study (gefitinib) was negative. By contrast, although Japanese patients, who have a high response rate to EGFR-TKIs, were used as the study subjects of the V15-32 study (gefitinib), the docetaxel control group tended to have better survival at each time point of 10-12 months after the beginning of treatment.

Table 2. RCTs (Randomized Clinical Trials) of Erlotinib & Gefitinib

	Early	Stage III	Advanced	
Erlotinib	RADIANT (n=945, vs. placebo, *on going*)		First line TALENT (n=1172, CDDP/GEM± Erlotinib, *negative*) TRIBUTE (n=1059, CBDCA/PTX± Erlotinib, *negative*) SATURN (n=850, CT x 4 → vs. placebo, *on going*)	Relapsed BR.21 (n=731, vs. placebo, *positive*) TITAN (n=648, vs DTX, *on going*)
Gefitinib	BR.19 (n=1242, vs. placebo, *terminated*) Japanese trial (n=670, vs. placebo, *terminated*)	SWOG0023 (n=840, CRT→DTX→gefitinib, *terminated*)	First line INTACT1 (n=1093, CDDP/GEM± Gefitinib, *negative*) INTACT2 (n=1037, CBDCA/PTX± Gefitinib, *negative*)	Relapsed ISEL (n=1692, vs. placebo, *negative*) V15-32 (n=484, vs. DTX, *negative*) INTEREST (n=1466, vs. DTX, *positive*)

4) In the SWOG S0023, which evaluated differences according to whether gefitinib was used after radiochemotherapy, survival time was significantly shorter in the gefitinib group(24). Reason. Although considerable patient selection was involved, it was a randomized controlled trial.

5) Do the results of the Interest and BR-21 studies suggest that the efficacy of gefitinib and erlotinib is equivalent?(21,27) Is it legitimate to speculate and argue whether there are differences in efficacy based on the results of clinical studies with completely different study designs.

These questions suggest that the basic assumptions underlying clinical trial results of anticancer drugs can not be applied to molecularly targeted therapy.

Against this background the following are conceivable.

1) The response rates of Western people and Asian people to EGFR-TKIs are different, and the reason for the difference is a difference in EGFR mutation rate(28～44).

2) At present it is unknown whether EGFR mutations are a predictor of the therapeutic efficacy of EGFR-TKIs or even a predictor of the therapeutic efficacy of cytotoxic anticancer drugs(26).

3) EGFR-TKIs display a potent antitumor effect in cells that possess the target, but have no effect at all on cells that do not possess it. By contrast, because cytotoxic anticancer drugs exert an antitumor effect against whole tumor mass (Fig. 1), the effect that they have on survival time is different from that of molecularly targeted drugs even if the response rates are equivalent according to the RECIST criteria (Fig. 2). The concept of "long NC" does not apply to molecularly targeted drugs such as EGFR-TKIs. Actually, in the V15-32 study the response rate to gefitinib was approximately twofold compared

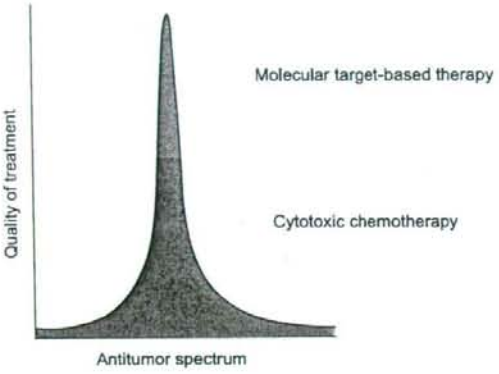


Fig. 1. Improvement of treatment quality.

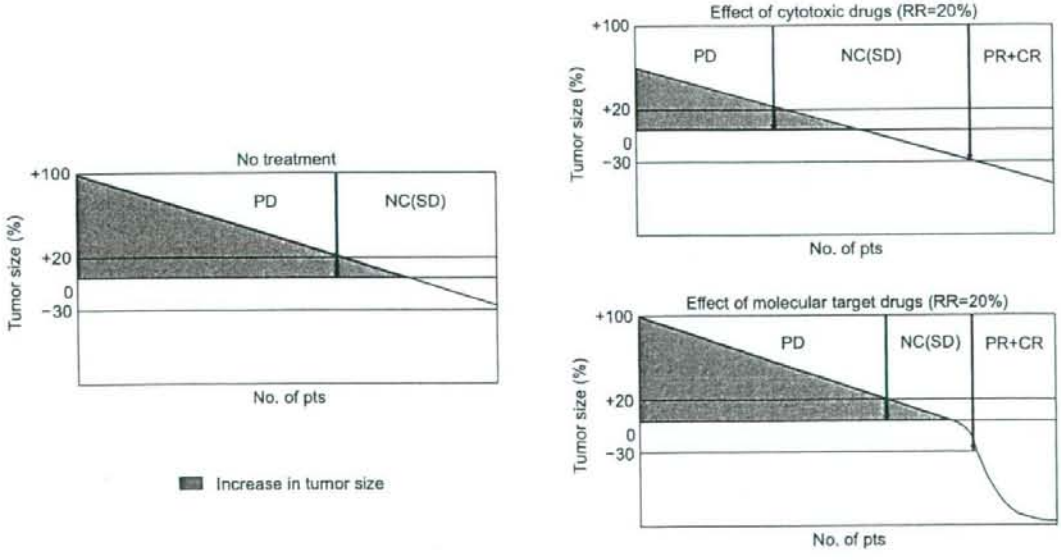


Fig. 2. Difference in the effect of cytotoxic drugs and molecular target drugs (waterfall plots).

with docetaxel(26), but non-inferiority could not be demonstrated, and survival time at each time point assessed in the gefitinib group was slightly poorer than in the docetaxel group at each time point during early phase after the beginning of treatment (Table 3, Fig. 3, 4). Waterfall plots are being used often recently. We can show the differences in efficacy between anticancer drugs and molecularly targeted drugs in figures (Fig. 2).

The basis of molecularly targeted therapy is that it should be used to treat patients who harbor the target. The problem lies in the degree of sensitivity and specificity of the biomarkers that are capable of detecting the molecular target. The molecular target of EGFR-TKIs is a mutated EGFR, and while a response rate of approximately 80% can be achieved when mutations are present, a response of 10% is obtained even when there are no mutations(28~32). Moreover, it is not easy to obtain samples that are sufficient to detect mutations. Attempts are being made to devise a method of detection that uses blood, etc., as the specimen, but the results have not been satisfactory. Changes in surrogate tissue seem merely to reflect germ line variation, and their meaning is different from that of assessments that use tumor tissue and reflect both germ line variation including SNPs and somatic mutation. Attempts have also been made to predict therapeutic efficacy on the basis of gene expression(40), protein expression(41), etc., in addition to mutations, but no reliable results have been reported.

Table 3. Overall Survival (ITT)

	Gefitinib	RR	Docetaxel	RR
No. of Pts	245	22.5%	244	12.8%
No. of events	156		150	
One year survival (%)	48%		54%	

Hazard ratio=1.12 (0.89~1.40) p=0.330. Non-inferiority could not be demonstrated.

Anti-EGFR Antibody

There have been few results of research on the effect of EGFR antibodies (cetuximab, panitumab, matuzumab) on lung cancer. The antibodies recognize epitopes on the cell surface and have been found to exert their antitumor activity by blocking signal transduction pathway or by antibody-dependent cell-mediated cytotoxicity (ADCC). The mechanism by which they block signal transduction systems has not been elucidated. According to the results of in vitro studies, the majority of the antitumor activity of the antibodies appears to be attributable

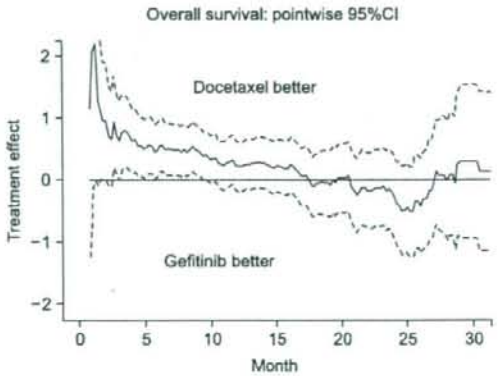
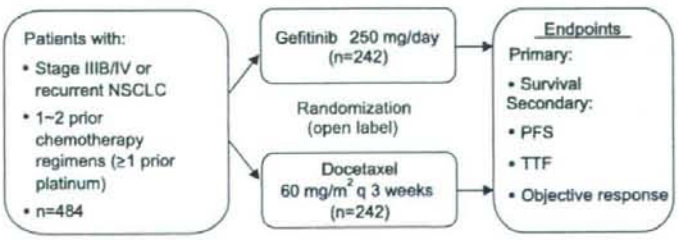


Fig. 4. Treatment effect at each time point. Analysed by Prof. Masahiro Takeuchi, Kitasato University, Division of Biostatistics & Division of Pharmaceutical Medicine. Courtesy of Prof. M. Takeuchi, Kitasato University.



- Stratified for histology, gender, PS, study site
- Non-inferiority design: Upper limit of hazard ratio<1.25

Fig. 3. Trial V15-32: Phase III trial of gefitinib vs. docetaxel in 2nd/3rd line NSCLC.

to ADCC. In a study comparing CDDP+vinorelbine±cetuximab, Gatzemeier and Rosell obtained an improvement in response rate and prolongation of progression-free time in comparison with anticancer drug therapy alone(45), and Kelley et al. conducted a study comparing simultaneous and consecutive treatment with cetuximab in combination with CBDCA+ paclitaxel and obtained better treatment results in the simultaneous administration group(46). Assessment of improvement in the results of treatment by applying EGFR antibodies to the treatment of other stages of lung cancer seems necessary in the future(47,48).

Anti-VEGF Antibody (Bevacizumab)

Anti-VEGF antibody is intended to improve treatment results by selectively modifying the molecular biological properties of the host that constitutes the tumor environment(49). When negative data for matrix metalloproteases persisted, it was concluded that "target-less molecularly targeted agents" that act on the tumor environment in this way do not contribute to improving the results of treatment. However, the remarkable improvement in results of treatment with IFL+bevacizumab for colorectal cancer(50) and reproducible results with FOLFOX4+ bevacizumab(51) suggested that even drugs that acted on the tumor environment could produce a significant survival benefit and improvement in cure rate. The ECOG reported positive data for PTL+CBDCA±bevacizumab(52,53) in previously untreated advanced non-small cell cancer, but despite strict patient selection that accepted only non-squamous cell carcinoma patients as subjects, a mere 2-month survival benefit and a significantly high rate of adverse effects, such as bleeding, were observed. The enormous cost of treatment was seen as another problem. The AVAIL study, which was primarily conducted in Europe, compared gemcitabine+CDDP±bevacizumab, and prolongation of progression-free time was observed in the bevacizumab group(54), but, unfortunately, there was no prolongation of overall survival time. Moreover, in the 7.5 mg/kg dosage group of the ECOG phase II trial, the results of treatment were poor. It is unknown whether these inconsistencies were simply attributable to differences in the prognostic factors of the patients entered in the study or were based on the chemotherapy regimen that was used. Research on biomarkers that might predict the efficacy of target-less molecularly targeted drugs or be correlated with their efficacy has been lagging. Bevacizumab has already begun to be used in Japan in combination with FOLFOX4 to treat colorectal cancer. Training of clinical oncologists who sufficiently understand the emergency management of thrombosis and bleeding is needed.

Multiple-target Molecularly Targeted Drugs ("Dirty" Targeted Drugs)

A great number of anticancer drugs that act on a variety of targets have been developed, and clinical trials have been conducted in lung cancer. From the standpoint of the process of drug development, the fact that a drug that selectively modifies a certain target has been developed does not necessarily mean that it will act on that target alone. Thus, viewed from the opposite vantage point, developing drugs that are designed to modify many targets just from the beginning may also serve as a strategy. Since signal transduction systems are constructed of complex networks, attempting to impede tumor growth by simultaneously inhibiting several of their pathways is one possible approach. However, as the number of targets increases, proof of principle studies become more difficult. In addition, it will be necessary to consider the choice between using dirty targeted drugs that have many targets or using combinations of targeted drugs that have different targets. Moreover, even being called "dirty" seems unavoidable, because many investigators themselves have not sorted out what the targets are in the clinical trials of Sorafenib(55), Sunitinib(56), Vandetanib(57), etc.(58), which are currently being tested. Every time results of clinical studies are obtained, there is a feeling that they are going to cause a headache. Selection of a population that possesses the target would seem essential for clinical studies of molecularly targeted drugs. On the other hand, because there are no targets for molecularly targeted drugs that are cancer-environment-specific, patient selection is not performed. Because the "dirty" targeted drugs that are currently being used are equipped with both functions, it is claimed that a combined effect can be achieved, but there is also a possibility that we are doing a biologically fatal contradiction.

Clinical Studies and Biomarkers

When molecularly targeted drugs were introduced, there was

a widespread theory that "because the efficacy of molecularly targeted drugs is exhibited in the form of a cytostatic effect instead of a cytotoxic effect, it is impossible to evaluate them by ordinary clinical trial methodology". However, the hypothesis has been demonstrated to be false. 1) despite being targeted therapy, effective compounds cause tumor shrinkage, 2) matrix metalloproteases and other drugs that act on the tumor environment have yielded negative data in phase 3 studies every single time, and 3) drug-specific adverse effects associated with increases in dose are observed with drugs other than antibodies, it now appears possible to evaluate molecularly targeted drugs by conventional clinical studies. Facts that have subsequently become clear include that 1) targeted drugs are effective only in cells that possess the target and are completely ineffective in cells that do not, 2) drugs that act downstream of signal transduction have poor selectivity, and it is difficult to demonstrate efficacy, and 3) drugs that act on specific molecular biological characteristics of the cancer environment in a certain sense do not have a target. Thus, when a specific molecular biological target is present on the cancer cells themselves, it seems ideal to select subjects who have the target and use it to treat them. Success has been achieved with Herceptin in breast cancer by using that strategy, and it is not difficult to plan clinical trials of Rituxan for lymphomas, Gleevec for CML, etc., because all of the cancer cells retain the original target. Patient selection for EGFR-TKIs seems to be the most strategic task, and the establishment of validated biomarkers with high sensitivity and excellent selectivity also seems to be an important task. V15-32 research has shown that it is impossible to predict survival curves in clinical studies that include whole patients without selection. By contrast, because drugs that act on the cancer environment, as represented by Avastin, do not have a target, all types of cancers are candidates for treatment. The exception is patients who develop severe toxicity. This category of drugs basically cannot be expected to be effective when used alone. They are used in combination, and cancer chemotherapy intensifying effects, etc., have been shown. Because these drugs can be expected to be effective to a certain degree in all patients without selection and they ultimately seem to intensify the efficacy of anticancer drugs, it seems possible to make comparisons by means of survival curves and proportional hazard models of treatment with cytocidal anticancer drugs.

CONCLUSION

Effect of Molecularly targeted therapy of lung cancer is less clear-cut than for other diseases. Despite EGFR-TKIs displaying a remarkable antitumor effect in taxane-platinum-resistant cases, it can be pointed out that it has been impossible to demonstrate any prolongation of survival time and that there are far too few segmented cases, especially in Western countries, in order to perform patient selection based on EGFR mutations.

Comparative studies in patients selected according to their clinical characteristics and whether they have EGFR mutations are currently being conducted, and it will be very interesting to see what kind of results they yield. Avastin seems likely to be approved in Japan, but caution is required in regard to toxicity. What kind of results will be obtained when "dirty" targeted drugs are subjected to clinical studies without patient selection is unknown territory.

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ORIGINAL REPORT

Phase II Trial of Preoperative Chemoradiotherapy Followed by Surgical Resection in Patients With Superior Sulcus Non–Small-Cell Lung Cancers: Report of Japan Clinical Oncology Group Trial 9806

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ABSTRACT

Purpose
To evaluate the safety and efficacy of preoperative chemoradiotherapy followed by surgical resection for superior sulcus tumors (SSTs).

Patients and Methods
Patients with pathologically documented non–small-cell lung cancer with invasion of the first rib or more superior chest wall were enrolled as eligible; those with distant metastasis, pleural dissemination, and/or mediastinal node involvement were excluded. Patients received two cycles of chemotherapy every 4 weeks as follows; mitomycin 8 mg/m^2 on day 1, vindesine 3 mg/m^2 on days 1 and 8, and cisplatin 80 mg/m^2 on day 1. Radiotherapy directed at the tumor and the ipsilateral supraclavicular nodes was started on day 2 of each course, at the total dose of 45 Gy in 25 fractions, with a 1-week split. Thoracotomy was undertaken 2 to 4 weeks after completion of the chemoradiotherapy. Those with unresectable disease received boost radiotherapy.

Results
From May 1999 to November 2002, 76 patients were enrolled, of whom 20 had T4 disease; 75 patients were fully assessable. Chemoradiotherapy was generally well tolerated. Fifty-seven patients (76%) underwent surgical resection, and pathologic complete resection was achieved in 51 patients (68%). There were 12 patients with pathologic complete response. Major postoperative morbidity, including chylothorax, empyema, pneumonitis, adult respiratory distress syndrome, and bleeding, was observed in eight patients. There were three treatment-related deaths, including two deaths owing to postsurgical complications and one death owing to sepsis during chemoradiotherapy. The disease-free and overall survival rates at 3 years were 49% and 61%, respectively; at 5 years, they were 45% and 56%, respectively.

Conclusion
This trimodality approach is safe and effective for the treatment of patients with SSTs.

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INTRODUCTION

Superior sulcus tumors (SSTs), involving structures at the thoracic inlet, represent a small subtype of non–small-cell lung carcinoma (NSCLC). These SSTs, first described by Henry Pancoast[1,2] and thus also called Pancoast tumors, have posed a challenging problem for surgeons, radiation oncologists, and medical oncologists alike, ever since they were first described.[3]

Preoperative radiotherapy has long been the community standard in the management of SSTs.[4-17] However, both the complete resection rate (approximately 50%) and long-term survival rate (approximately 30%) have remained poor and unchanged over the last 40 years, since the first treatment strategy was reported in the 1960s. Local control has remained the main problem,[15,17,18] adversely affecting quality of life as well as survival of patients. Presence of mediastinal lymph node metastasis (N2 status) has been reported to be associated with a particularly poor prognosis.[9,18]

However, a series of clinical trials over the last two decades have shown concurrent chemoradiotherapy to be beneficial in the treatment of unresectable stage III NSCLC.[19-21] The addition of chemotherapy to thoracic radiotherapy seems to suppress distant micrometastases,[22,23] and giving

concurrent chemotherapy with radiotherapy has been shown to yield improved local control[19,24] with survival benefit.

Encouraged by the promising data of concurrent chemoradiotherapy for N2 NSCLC, the Southwest Oncology Group (SWOG) applied this modality as preoperative therapy for patients with SSTs (SWOG 9416, Intergroup Trial 0160), and reported favorable results.[25]

The Japan Clinical Oncology Group (JCOG) launched another trial of this preoperative concurrent chemoradiotherapy, or the trimodality approach, for the treatment of SSTs in 1999, before the first report of SWOG 9416 was published. Our study was initiated to evaluate the safety and efficacy of this treatment strategy in this rare subset of patients with NSCLC. As the induction treatment, we used mitomycin, vindesine, and cisplatin (MVP) combination chemotherapy, which has been demonstrated to be safe and effective for concurrent chemotherapy with thoracic radiotherapy in Japanese trials.[19]

PATIENTS AND METHODS

Eligibility Criteria

Patients with untreated histologically or cytologically documented NSCLC involving the superior sulcus with clinical stage T3 or T4 disease were eligible for entry onto this study. T4 diseases included tumor invasion to the spine (including to a transverse process of vertebra), aorta, or superior vena cava; invasion to the chest wall or subclavian vessels was included in T3 disease. Involvement of the superior sulcus was confirmed by computed tomographic (CT) or magnetic resonance imaging (MRI) evidence of tumor invasion of the first rib or more superior chest wall. Patients with pleural or pericardial dissemination, malignant effusion, and/or distant metastasis (M1) were excluded. Those with clinical N2 disease (mediastinal node involvement) were also excluded; all mediastinal nodes measuring $\geq$ 1.0 cm in size on CT images were required to be biopsied and documented to be negative for metastasis before patient enrollment. However, those with ipsilateral supraclavicular node involvement (N3) were eligible, unless it was accompanied by mediastinal node metastasis. Each patient was required to fulfill the following criteria: 15 to 74 years of age, Eastern Cooperative Oncology Group performance status of 0 to 1; adequate organ function (ie, leukocyte count $\geq$ 4,000/μL, platelet count $\geq 10^5/\mu$L, hemoglobin $\geq$ 11.0 g/dL, serum creatinine less than 1.5 mg/dL, creatinine clearance $\geq$ 60 mL/min, serum bilirubin less than 1.5 mg/dL, serum ALT and AST less than double the upper limit of the institutional normal range, arterial partial pressure of oxygen $\geq$ 70 mmHg, and predicted postoperative forced expiratory volume in 1 second $\geq$ 0.8 L. From July 2001, when the protocol was revised after the death of a patient from septic shock during chemoradiotherapy, those patients with systemic use of corticosteroids were excluded.

Patient eligibility was confirmed by the JCOG Data Center before patient registration. This study was approved by the institutional review boards at each participating center, and written informed consent was obtained from all patients.

Treatment Plan

Induction chemotherapy. Patients received two courses of MVP combination chemotherapy with a 4-week interval in between. Mitomycin was administered at 8 mg/m^2 on chemotherapy day 1, and vindesine was administered at 3 mg/m^2 on days 1 and 8; both were administered as bolus injections. Cisplatin was administered at 80 mg/m^2 as a 2-hour infusion on day 1, with ample hydration and antiemetic administration.

The second cycle of chemotherapy was postponed until all the severe toxicities recovered to grade 1 or 0. If the second cycle could not be started within 2 weeks of the due date, it was canceled, and the patient received only preoperative radiotherapy, if possible.

Induction radiotherapy. Thoracic radiotherapy was started with a linear accelerator ($\geq$ 4 MeV) on chemotherapy day 2. The first session was scheduled to be given with the first chemotherapy cycle at 27 Gy in 15 fractions over 3 weeks. Then the second session was started after a week's interval until day 2 of the second course of chemotherapy. The second session, given with the second cycle of MVP, was administered at 18 Gy in 10 fractions over 2 weeks. The total radiation dose was thus 45 Gy in 25 fractions administered over 6 weeks, including the 1-week split, or interval, between the two sessions; this schedule, including the split, basically followed that of the original method reported by Furuse et al.[19] The radiation field included the primary tumor and the ipsilateral supraclavicular nodes. The mediastinal and hilar nodes were not irradiated, even in cases with hilar node involvement (clinical N1 cases).

Surgery. After the induction chemoradiotherapy, each case was re-evaluated to determine the clinical response and resectability. The resectability of the tumor was determined by the multimodality team of each institution, irrespective of the clinical response (tumor shrinkage). Surgical resection of the tumor was performed 2 to 4 weeks after the completion of the induction therapy. The surgical procedures undertaken included lobectomy or pneumonectomy, with systematic node dissection. Standard systematic node dissection, ND2, includes complete removal of the hilar and mediastinal nodes. Less complete dissection includes ND0 (ie, no systematic dissection with or without lymph node sampling) or ND1 (ie, hilar node dissection with or without mediastinal lymph node sampling).

Boost therapy. For unresected or incompletely resected cases, boost radiotherapy of 21.6 Gy in 12 fractions was given. Those who were judged to have undergone complete resection were followed up without additional therapy until clinical evidence of recurrence.

Patient Evaluation and Follow-Up

Before enrollment onto the study, each patient underwent complete medical history taking and physical examination, blood cell count determinations, serum biochemistry testing, arterial blood gas analysis, chest x-ray, ECG, CT scan of the chest, bronchoscopy, CT scan or ultrasound of the upper abdomen, whole-brain CT or MRI, and an isotope bone scan. Chest MRI was recommended for evaluation of the local tumor status but was not mandatory. Blood cell counts, serum biochemistry testing, and chest x-ray were performed weekly during each course of chemotherapy. Chest CT was performed every 3 to 4 weeks during the induction therapy.

Chemotherapy toxicity was evaluated according to the JCOG Toxicity Criteria,[26] modified from the National Cancer Institute Common Toxicity Criteria version 1. Tumor responses were assessed radiographically according to the standard, two-dimensional WHO criteria[27] and were classified into complete response (CR), partial response, no change, progressive disease (PD), and not assessable. Response confirmation at 4 weeks or longer intervals was not necessitated. After curative resection and/or definitive boost radiotherapy, the patients were followed up with periodic re-evaluation, including with chest CT, as well as a systemic survey every 6 months for the first 3 years.

Central Review

Radiographic reviews for eligibility of the enrolled patients and the clinical responses were performed at the time of the JCOG Lung Cancer Surgical Study Group meeting, held every 3 to 4 months. The study coordinator (H.K., a medical oncologist), the group coordinator (M.T., a surgical oncologist), and a few selected investigators of the group reviewed the radiographic films. The clinical response data presented below were all confirmed by this central review.

Statistical Considerations

The primary end point of the study was the survival rate at 3 years. The sample size calculation was performed, as described in Appendix 1 (online only).

Secondary end points included the objective tumor response to chemotherapy, complete resection rate, and postsurgical morbidity/mortality. Both overall survival (OS) and progression-free survival (PFS) were calculated from the date of enrollment by the Kaplan-Meier method. For exploratory analysis to identify prognostic factors, the OS or PFS of subgroups was compared by two-sided log-rank tests. All analyses were performed with the SAS software version 8.2 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

From May 1999 to November 2002, 76 patients from 19 institutions were enrolled onto the study. Three patients were ineligible. One patient was found to have concomitant anemia and did not receive the protocol treatment. Two others were found ineligible by the central review, after completion of the protocol therapy; the tumor was judged not to involve the first rib in one case, and in the other, a mediastinal node was judged to be enlarged on chest CT, without confirmation by mediastinoscopy. These two cases were included in the analysis. Therefore, 75 patients were analyzed to determine the toxicities, response rates, surgical and pathologic results, PFS, and OS. All 76 patients were included in the analysis of the patient characteristics, as shown in Table 1. In each of the T4 cases, the tumor was judged to have involved the spine. Nodal status was clinically determined and was pathologically confirmed in only a few cases.

Induction Therapy Delivery and Toxicity

The study schema with the actual numbers of patients receiving the protocol therapy is shown in Appendix Figure A1 (online only).

Table 1. Patient Characteristics (n = 76)

Characteristic	No. of Patients	%
Sex		
Male	67	88
Female	9	12
Age, years		
Median	57.5	
Range	34-74	
ECOG performance status		
0	30	39
1	46	61
Clinical T stage		
T3	56	74
T4	20	26
Clinical N stage		
N0	59	78
N1	9	12
N2*	1	1
N3	7	9
Smoking history		
No	4	5
Yes	72	95
Median smoking history	1.5 packs for 37 years	
Body weight loss within 6 months		
≤ 5%	61	80
5-10%	7	9
> 10%	5	7
Missing	3	4
Histology		
Adenocarcinoma	34	45
Squamous cell carcinoma	27	36
Others/unclassified	15	20
Primary site		
Right	39	51
Left	37	49

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Found ineligible by central review but included in the subsequent analyses.

The induction therapy could be completed in 71 (95%) of the 75 patients. The treatment was terminated in the remaining four patients after only one course of chemotherapy (owing to the development of adverse events in two cases, patient refusal in one case, and early toxicity-related death in one case).

Table 2 lists the major toxicities of the protocol therapy. They were mainly hematologic, and although more than 80% of the patients experienced neutropenia/leukopenia, they were generally transient and not complicated by infection/fever. Overall, toxicities were well tolerated. There was one toxic death on chemoradiotherapy day 6 as a result of severe myelosuppression and subsequent development of septic shock.

Clinical Response to the Induction Therapy

The clinical responses of the 75 eligible patients to induction therapy were judged radiologically and confirmed by the central review. The responses were as follows: CR, 0 patients; partial response, 46 patients; no change, 22 patients; PD, five patients; not assessable, two patients. The overall response rate was 61% (95% CI, 49% to 72%).

Surgical and Pathologic Results

Thoracotomy was performed in 57 (76%) of the 75 patients who received the induction therapy. The surgical procedures undertaken

Table 2. Major Toxicities of Induction Therapy (N = 75) and Postsurgical Complications

Toxicity or Complication	No. of Patients			% Grade 3/4
	Grade 1/2	Grade 3	Grade 4	
Acute toxicity*				
Leukopenia	1/11	37	26†	84
Neutropenia	3/9	26	36†	83
Anemia	19/47	5	0	7
Thrombocytopenia	14/12	9	2†	15
ALT	27/5	2	0	3
Creatinine	18/2	0	0	0
PaO_2	37/6	0	0	0
Emesis	32/25	2	— (not defined)	3
Diarrhea	7/5	1	0	1
Constipation	22/3	1	0	1
Esophagitis	22/9	0	0	0
Infection	10/9	6	1†	9
Neuropathy	8/0	0	— (not defined)	0
Skin toxicity	16/2	1	0	1
Fever	25/19	1	1	3
Postsurgical complications‡				
ARDS	0	1	1 (grade 5)	
Empyema	0	2	0	
Cylothorax	1	1	0	
Pneumonitis	0	1	0	
Late complications‡				
Pneumonitis	0	1	0	
Bleeding	0	0	1 (grade 5)	

Abbreviations: PaO_2, alveolar-arterial difference in partial pressure of oxygen; ARDS, adult respiratory distress syndrome.
*During induction therapy.
†Includes one patient with toxic death owing to septic shock.
‡Report of each complication was evaluated by National Cancer Institute Common Toxicity Criteria version 3.0.

were as follows: lobectomy, 53 patients; partial resection, three patients; exploratory thoracotomy, one patient; none of the cases required pneumonectomy. Combined resection of the chest wall was undertaken in 51 of the 57 patients. Complete mediastinal lymph node dissection (ND2) was performed in 42 patients, and the remaining 15 patients underwent less extensive dissection or sampling (ND0 or ND1).

The results of thoracotomy were as follows: gross residual tumor (R2 resection, including one with probe thoracotomy), three patients; microscopically residual tumor on pathologic review (R1 resection), three patients; complete surgical and pathologic resection (R0 resection), 51 patients. Pathologic downstaging of the tumor as compared with the clinical stage before induction therapy was achieved in 23 patients (40% of the patients who underwent surgery); this is an inherently inaccurate figure and should be interpreted as such, owing to the lack of pathologic confirmation of the c stage at presentation. Pathologic CR, with no residual viable tumor cells in the resected specimens, was achieved in 12 patients (16% of the 75 treated patients). Table 3 lists the surgical and pathologic results according to the initial clinical T factor.

The major postoperative morbidities included adult respiratory distress syndrome (ARDS) in two patients, empyema in two patients, chylothorax in two patients, and pneumonitis in two patients. One patient died of sudden major bleeding on postoperative day 24. The bleeding was identified at autopsy as being from an intercostal artery. Another patient died of ARDS after off-protocol pneumonectomy. The patient had been judged to have PD in response to the induction therapy as a result of emergence of intrapulmonary metastases. The attending surgeon and the patient agreed to salvage surgery, and the patient developed postoperative ARDS.

Thus the total number of toxic deaths was three, including one caused by septic shock during the induction, one by delayed postoperative bleeding, and one by the development of ARDS after off-protocol, salvage surgery.

Table 3. Surgical and Pathologic Results According to Initial Clinical T Stage

Characteristic	c-T3	c-T4
No. of patients	55	20
No surgery performed		
No.	7	11
%	13	55
Reason for no surgery		
Protocol violation	0	1
Toxic death	0	1
Adverse event	0	1
Progressive disease	2	2
Judged unresectable	0	3
Patient refusal	5	3
Surgical procedures		
Thoracotomy		
No.	48	9
%	87	45
Pneumonectomy	0	0
Lobectomy	45	8
Probe thoracotomy	1	0
Other	2	1
With combined resection	44	7
Rib	38	6
Parietal pleura	4	1
Vertebra	3	3
Major vessel	3	0
Clavicle	1	0
Completeness of resection		
R2 operation	2	1
R1 operation	3	0
R0 operation		
No.	43	8
%	78	40
Pathologic results		
Downstaging	18	5
Pathlogic complete response	9	3

Boost Therapy

Boost radiotherapy was given to 15 patients, including 12 of the 15 patients in whom thoracotomy was not performed after the completion of induction chemoradiotherapy. One patient received boost radiotherapy after grossly incomplete resection, and another received boost radiotherapy after gross complete resection with microscopically residual disease. In 12 of the 15 patients, boost radiotherapy was completed with a total dose of 66.6 Gy.

PFS and OS

Figures 1 and 2 show the PFS and OS curves, updated in November 2006. Forty-one patients were alive, with a median follow-up period of 68 months. The median PFS time was 28 months. The PFS rates at 3 and 5 years were 49% and 45%, respectively. The median OS has not yet been reached. The OS at 3 and 5 years were 61% and 56%, respectively. Subset analysis (Appendix Figs A2 through A5, online only) revealed that clinical T stage was a prognostic factor (Appendix Fig A2). Patients with clinical T3 disease had better outcome than those with clinical T4 disease (the survival rates at 3 and 5 years were 69% and 61%, respectively, versus 40% and 40%, respectively; log-rank $P = .031$). The clinical N stage and histologic type of the tumor did not significantly affect the OS (Appendix Figs A3 and A4) or PFS. As expected, the survival rate was good in patients in whom complete resection could be achieved, with a projected 5-year OS of 70% as compared with 24% in whom complete resection could not be

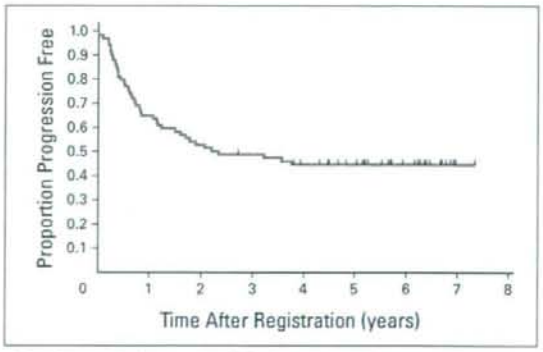

Fig 1. Progression-free survival (PFS) of the 75 eligible patients. PFS at 3 years and 5 years was 49% (95% CI, 38% to 60%) and 45% (95% CI, 34% to 56%), respectively, with a median PFS of 27.7 months.

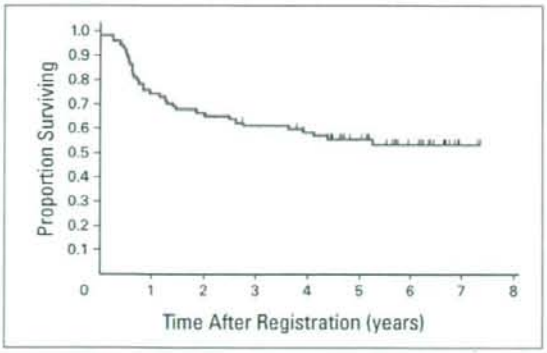

Fig 2. Overall survival (OS) of the 75 eligible patients. OS at 3 years and 5 years was 61% (95% CI, 49% to 71%) and 56% (95% CI, 44% to 66%), respectively. The median OS has not been reached.

achieved (Appendix Fig A5). The survival of the 12 patients with pathologic CR was especially favorable (Appendix Fig A6, online only).

Pattern of Relapse

So far, 39 patients have experienced tumor relapse. Table 4 lists the initial relapse sites, according to the curative extent of the surgical resection. For unresected or incompletely resected cases, locoregional relapse was predominant. To the contrary, for completely resected cases, relapse at distant sites was the most frequent relapse pattern, with some brain-only relapse patients.

DISCUSSION

We conducted a multi-institutional phase II trial of a trimodality approach, namely, preoperative chemoradiotherapy followed by surgical resection, in patients with SSTs. Because of the rarity of this subtype of NSCLC, no randomized trial has been conducted previously.[28] Our report is the second of a large-scale, prospective trial after SWOG 9416/INT 0160 and reproduced its favorable outcomes.[25]

The long-term results of the SWOG 9416/INT 0160 trial were recently published.[29] Although the chemotherapy regimens used were different, a standard classic platinum-based combination was used in both. The preoperative radiotherapy doses were also identical (45 Gy), although a 1-week split (interval between two sessions) was included in our protocol (but not in the SWOG trial). Boost chemotherapy was planned after curative resection in the SWOG trial, but the compliance rate was poor,[25] as in other perioperative therapy reports; we had anticipated that the majority of the patients would not be fit enough for additional toxic therapy after a major thoracic surgery and did not include it in our protocol.

Table 4. Initial Relapse Sites

Relapse Site	Patients With Complete Resection (n = 51)	Patients Without Complete Resection (n = 24)	Total (N = 75)
Locoregional* only	2	8	10
Distant only	14	6	20
Brain only	4	1	5
Both	4	5	9
Total	20	19	39

*Locoregional = surgical margin, within radiation field, hilar lymph nodes, mediastinal lymph nodes, supraclavicular lymph nodes.

Despite these minor differences, the results of the two trials were strikingly similar (Table A1, online only). The radiologic response rate was higher, whereas the pathologic CR rate was lower in our trial, but the differences were probably not clinically relevant, considering interobserver differences in the response evaluation and the well-known discrepancy between clinical versus pathologic effects. The intensive trimodality approach was found to be feasible in both reports, with a reasonably low toxic death rate of 4%. The resection rate, which had remained unchanged at approximately 50% for almost 40 years with conventional preoperative radiotherapy, was approximately 70% in both studies. Particularly noteworthy was the reproducibility of the favorable survival data, with a 5-year OS rate of 44% in the United States trial and 56% in our trial, which were clearly superior to the historical value of 30%.[3,25]

A shift in the trend of clinical problems also became clear.[25,28,29] The relapse patterns changed from predominantly locoregional[17,18] to mainly distant recurrences in cases with complete resection,[25,28,29] and a significant number of such patients suffered from metastasis in the brain as the initial site of relapse.[29] To the contrary, complete resection could be achieved in less than half of the patients with c-T4 disease, and neither local control nor long-term survival was satisfactory in those in whom it could not be achieved. It seems that there might be room for improvement in radiotherapy.

Several questions remain unresolved. One is that of management of patients with mediastinal node involvement. These clinical N2 cases have been known to have the poorest prognosis[9,18] and were excluded from both the SWOG and JCOG trials. Although trimodality approaches have been reported in cases with clinical N2 stage NSCLC,[30,31] inclusion of the hilar and mediastinal nodes in the irradiation field increased the toxicity risk to an unacceptable level in our prior phase II trial (JCOG 9805).[32]

In addition to the unresolved questions above, our study also had a critical limitation. Although this was a prospective, large-scale, and multi-institutional trial, no definite conclusions could be obtained from the single-arm phase II study. As repeatedly pointed out, however, a phase III trial would be unrealistic due to the rarity of SSTs. Possibly, clinical questions common with other patient subsets could be tested in a phase III trial targeting a broader patient population; for example, patients with SSTs and other stage III NSCLC could be enrolled onto a phase III trial of prophylactic cranial irradiation after definitive induction therapy.[33]

In conclusion, we report a favorable outcome of preoperative chemoradiotherapy in patients with SSTs, confirming the results of the previous SWOG/Intergroup trial. We believe that this strategy may be acceptable as standard for the treatment of this disease and also serves as a reference for future trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

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

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Efficacy and Safety of Pemetrexed in Combination with Cisplatin for Malignant Pleural Mesothelioma: A Phase I/II Study in Japanese Patients

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Background: Pemetrexed in combination with cisplatin (Pem/Cis) is used globally for the treatment of malignant pleural mesothelioma (MPM). This Phase I/II study was conducted to determine the recommended dose (RD) (Phase I) of Pem/Cis, and evaluate the efficacy and safety (Phase II) in Japanese MPM patients.

Methods: Key eligibility criteria were histologic diagnosis of MPM incurable by surgery, no prior chemotherapy, and a performance status 0–1. Under full vitamin supplementation, pemetrexed was intravenously administered on Day 1 of a 21-day cycle, followed by cisplatin. A cohort of six patients, starting from pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 (Level 1), were studied in the dose-escalation Phase I (Step 1). The RD determined in Step 1 was carried forward into Phase II (Step 2). Planned number of patients treated with Pem/Cis was 18–38.

Results: In Step 1, 13 patients were enrolled: seven in Level 1 and six in Level −1 (pemetrexed 500 mg/m^2, cisplatin 60 mg/m^2). Two of six evaluable patients had dose-limiting toxicities (pneumonitis and neutropenia) in Level 1, establishing Level 1 as the RD. In Step 2, 12 patients were enrolled, for a total of 19 patients treated at the RD. Seven patients achieved a partial response among these patients, for a response rate of 36.8% (95% confidence interval: 16.3–61.6); overall survival was 7.3 months. One drug-related death occurred due to worsening of a pre-existing pneumonia. Common grade 3/4 toxicities were neutropenia and decreased-hemoglobin.

Conclusion: The Pem/Cis combination provides promising activity and an acceptable safety profile for chemonaive Japanese MPM patients with the same recommend dosage and schedule used in rest of the world.

Key words: cisplatin – mesothelioma – pemetrexed – phase I/II

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a tumor derived from the mesothelium covering the surface of pleural membranes or from undifferentiated mesenchymal cells in connective tissue under the membranes. MPM is a locally invasive and aggressive tumor with a poor prognosis and a median survival time (MST) of ≈9–16 months (1).

MPM is known to be linked to asbestos exposure, and the incidence of this tumor is expected to increase in the next 10–20 years according to an estimation of asbestos consumption in

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the world (9). Recently, the prevalence of MPM in Japan was widely recognized after uncovering the high incidence of MPM and MPM-related deaths in ex-workers of asbestos factories and in residents of the surrounding areas who may have been subject to non-occupational exposure to asbestos fibers.

Surgical resection offers local control of the tumor but its effect on survival remains unclear. In addition, application of radiation therapy is limited because of the diffuse extension of tumor spread. Regimens applied to lung cancer such as platinum-containing chemotherapy have been used for MPM in Japan; however, the efficacy outcomes of these therapies are not satisfactory. Therefore, effective systemic chemotherapy for MPM is clearly needed.

Pemetrexed is a novel antifolate (12) that inhibits three enzymes in folate metabolism: thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase (11). Because of the multi-targeted profile of this compound, broad and preferable anti-tumor activity is expected. Pemetrexed has shown clinical activity in various tumors including mesotheliomas (6). A pivotal multicenter, randomized Phase III study of pemetrexed (500 mg/m^2) in combination with cisplatin (75 mg/m^2) versus cisplatin alone (cisplatin 75 mg/m^2) in patients with MPM who had no prior chemotherapy was conducted in 20 countries (not including Japan) (16). A total of 448 patients were randomized and treated in this study (226 treated by pemetrexed/cisplatin (Pem/Cis) and 222 treated by cisplatin). MST in the Pem/Cis arm was 12.1 months compared with 9.3 months in the cisplatin arm ($P = 0.020$, two-sided log rank test). This was the first confirmation of significant prolongation of survival for patients with MPM. On the basis of this evidence, the combination of pemetrexed and cisplatin was approved for the treatment of MPM in the USA in 2004. Since then, the combination therapy has been approved in more than 80 countries and regions for the treatment of MPM, and recognized as a standard care for MPM (8).

In 2005, we initiated a Phase I/II study of Pem/Cis therapy in Japanese patients with MPM who had no prior chemotherapy. The primary objectives of this study were to determine the clinically recommended dose (RD) of Pem/Cis therapy in the Phase I portion of the study (Step 1), and to examine tumor response of the combination therapy in the Phase II portion (Step 2). The secondary objectives included time-to-event efficacy outcomes [the duration of response, progression free survival (PFS), and overall survival time], 1-year survival rate, quality of life (QOL) assessments, pulmonary function tests and safety.

PATIENTS AND METHODS

Patient selection

Chemonaive patients with histological diagnosis of MPM, regardless of clinical stage and who were not candidates for curative surgery, were assessed for eligibility. Eligible patients needed to be 20–74 years old with a life expectancy $\geq$12 weeks and an Eastern Cooperative Oncology Group performance status (PS) 0 or 1. Patients were also required to have adequate organ functions: bone marrow reserve [platelets $\geq 100 \times 10^3/mm^3$, hemoglobin $\geq$9.0 g/dl, and absolute neutrophil count (ANC) $\geq 2.0 \times 10^3/mm^3$], hepatic function [bilirubin $\leq$1.5 $\times$ upper limit of normal (ULN), aspartate/alanine transaminase (AST/ALT) $\leq$2.5 $\times$ ULN, and serum albumin $\geq$2.5 g/dl], renal function (serum creatinine $\leq$ULN, and calculated creatinine clearance $\geq$45 ml/min using the Cockcroft and Gault formula), lung function (functional oxygen saturation [SpO_2] $\geq$92%) and normal electrocardiogram.

Patients were excluded from this study for active infection, symptomatic brain metastasis, a wide-spread diffuse shadow in the lung caused by interstitial pneumonitis diagnosed by chest X-ray, pregnancy, serious concomitant systemic disorders incompatible with the study, clinically significant effusions, Common Terminology Criteria for Adverse Events (CTCAEs) v3 grade $\geq$2 peripheral neuropathy, the inability to discontinue aspirin and other non-steroidal anti-inflammatory agents or the inability or unwillingness to take folate and vitamin B_{12} during the study.

This study was conducted in compliance with the guidelines of good clinical practice and the Declaration of Helsinki, and it was approved by the local institutional review boards. All patients gave written informed consent before study entry. The Efficacy and Safety Evaluation Committee (ESEC), an independent body, was consulted if any efficacy and safety issues arose in the study.

Study Design

This was a Phase I/II, multicenter, single-arm, open-label study, performed in two steps. The RD level established in Step 1 was carried forward in Step 2. Patients enrolled in Step 1 at the RD level could continue in Step 2 unless otherwise indicated. The planned number of patients in total of Steps 1 and 2 treated with Pem/Cis was 18–38 for examination of efficacy and safety profile. In Step 1, six patients were to be enrolled in each dose level. The lower number of the planned number of patients, 18, was set as the minimum number of patients needed to confirm that the response rate of the study drugs was significantly larger than the threshold rate of 10% at one-sided significant level 0.05 with $\geq$80% power.

Study Treatment

Pemetrexed was intravenously administered as a 10-min infusion on Day 1 of a 21-day cycle, followed by cisplatin administration intravenously as a 2-h infusion 30 min after pemetrexed administration. Patients were instructed to take a daily 1 g multivitamin containing 500 μg of folate beginning 1 week prior to Day 1 of Cycle 1 until study discontinuation. Vitamin B_{12} (1000 μg) was intramuscularly injected, starting 1 week prior to Day 1 of Cycle 1 and repeated every 9 weeks until study discontinuation. Patients remained on study unless they were discontinued, for instance, due to disease progression and unacceptable adverse events.

Determination of RD for Step 2

In Step 1 (Phase I), four escalating dose levels were planned: pemetrexed at 500 (Level 1), 700 (Level 2), 900 (Level 3) and 1000 mg/m^2 (Level 4) with cisplatin held at 75 mg/m^2. In addition, a lower dose level (Level −1) was planned at pemetrexed 500 mg/m^2 and a lower dose of cisplatin 60 mg/m^2 for a failure case of dose-escalation in Level 1. In the dose-escalation procedure, the starting dose of pemetrexed was set to be 500 mg/m^2 which is ca. 40% of the maximum tolerated dose (MTD) of pemetrexed monotherapy with folic acid and vitamin B_{12} supplementation determined in a Japanese Phase I study; the MTD and RD of pemetrexed were determined to be 1200 and 1000 mg/m^2, respectively (7). The percentage of the starting dose to the MTD was based on a guideline for Phase I/II study on anticancer drugs (10). For escalation of pemetrexed dose, a modified Fibonacci dose-escalation method was used (2). Dose level reduction or escalation depended on the incidence of dose-limiting toxicity (DLT) at a given dose level (Fig. 1). If two of six patients at Levels 1, 2 or 3 developed DLT, that dose level was considered the RD for Step 2 (Phase II) of the study, and then Step 2 was initiated. This was also the case for Level −1 or 4 if 0–2 patients developed DLT. If three or more patients developed DLT at a given dose level (except dose Level −1), the next lower dose level was considered the RD level for Step 2. If three or more patients had DLT at Level −1, a decision was made as to whether the study should be continued.

A DLT was defined as a toxicity occurring in Cycle 1 meeting one of the following criteria: any grade ≥3 non-hematologic toxicity (except nausea, vomiting, anorexia and fatigue), grade ≥2 peripheral neuropathy or hearing loss/impairment, grade ≥3 febrile neutropenia (<1000/mm^3 with ≥38.5°C), grade 4 leukopenia (<1000/mm^3) or neutropenia (<500/mm^3) lasting ≥3 days, thrombocytopenia (<25000/mm^3), or thrombocytopenia requiring platelet transfusion. A failure to start the second cycle by Day 29 due to toxicity was also considered a DLT. All toxicities were assessed according to CTCAE.

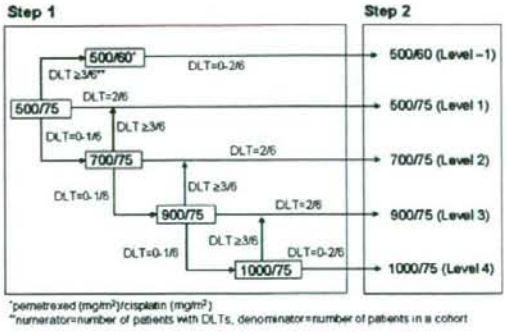

Figure 1. Scheme of dose-escalation Steps 1 and 2. DLT, dose-limiting toxicity.

Treatment Assessments

Anti-tumor Activity

Disease staging was assessed according to International Mesothelioma Interesting Group Tumor Node Metastasis (IMIG TNM) staging criteria (13). Within 28 days before the first treatment and approximately every 4 weeks after the first treatment, computer tomography or X-ray imaging of each lesion was performed. Tumor response was assessed using the modified Southwest Oncology Group (SWOG) criteria. Unidimensionally measurable lesions were defined as *Measurable disease*, and assessed objectively by the sum of the greatest diameters of them. Bidimensionally measurable lesions defined in the standard SWOG criteria (5) were assessed in the similar way. Best overall response selected from total overall response assessments was determined according to assessment of the Extramural Case Judgment Committee (E-CJC). Duration of response was measured as from the date of the first objective assessment of complete response (CR) or partial response (PR) until the date of the first assessment of progression of disease (PD). PFS was measured as from the registration date of Cycle 1 treatment until the first date of PD or death from any cause. Overall survival time was measured as from the registration date of Cycle 1 treatment until the date of death from any cause or until the last follow-up date in survival surveillance period.

QOL Assessments and Pulmonary Function Tests

QOL surveillance was employed using the following questionnaires: QOL questionnaire for cancer patients treated with anticancer drugs (QOL-ACD), and functional assessment of cancer therapy for lung cancer (FACT-L). These questionnaires were used on Day 1 of Cycles 1 and 2, and on 3 months after Day 1 of Cycle 1. QOL-ACD consists of four subscales (activity, physical condition, psychological condition and social relationships) and a total QOL scale (face scale) (4). The lung cancer subscale (LCS) score of FACT-L was used (3). As pulmonary function tests, forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and vital capacity (VC) were measured using a spirometer in the sitting position. All tests followed the Japanese Respiratory Function Test guidelines (14).

Safety

Adverse events were recorded throughout the study and after the last drug administration until signs of recovery were evident. Adverse events were evaluated according to treatment-emergent adverse events (TEAEs) definitions, and coded using the Medical Dictionary for Regulatory Activities (MedDRA v9.0). The severity (grade) of an adverse event was assessed according to CTCAE v3.

Statistical Analysis

The evaluation period of efficacy and safety in this study was defined as from the beginning of the study treatment to 5 months after the last patient began study treatment. For the

evaluations of overall survival time and 1-year survival rate, survival surveillance period was defined as from the beginning of the study treatment to 1 year after the last patient began study treatment. Patients who received the study drugs and complied with all inclusion/exclusion criteria were included in full analysis set (FAS). Patients who were treated with the RD level in Step 1 or 2 among FAS were included in efficacy analysis set for efficacy evaluation. Patients who received the study drugs at least once were included in safety analysis set for safety evaluation.

Assessment results of the best overall response by the E-CJC were used for efficacy analysis. Statistical tests based on binominal distribution were done to confirm that the response rate of the study drugs was significantly larger than the threshold rate of 10% at one-sided significant level 0.05. The threshold rate 10% was set on the basis of historical data on the response rate of cisplatin alone arm reported in other studies (15,16).

RESULTS

Patient Characteristics

From 2005 to 2006, a total of 25 Japanese patients with MPM were enrolled in Steps 1 and 2 at seven centers in Japan. All patients met the eligibility criteria and received study treatment; all were included in FAS. One patient was still receiving the study drug at the time of the efficacy and safety evaluations in this report.

Patient characteristics are summarized in Table 1. The majority of patients were male (22 patients, 88.0%). The median age was 61 years (range: 50–74 years). Most patients had a PS of 1 (18 patients, 72.0%) and clinical stage IV (21 patients, 84.0%). The predominant histologic subtype was epithelial in 64% of patients. Two demographic characteristics showed differences among dose levels. There were more patients with PS 0 in Level −1 (50.0%) than in Level 1 (21.1%). All six (100%) patients in Level −1 had the epithelial subtype versus 10 (52.6%) patients in Level 1.

Table 1. Patient characteristics

	Step 1 Level −1 ($n = 6$)	Level 1 ($n = 19$)	All treated ($n = 25$)
Gender			
Male	5	17	22
Female	1	2	3
Age			
Mean	61	61	61
SD	3.9	6.3	5.8
Med	61	59	61
Weight(kg)			
Mean	62.8	58.1	59.2
SD	8.51	11.19	10.65
Performance status prior to Cycle 1			
0	3	4	7
1	3	15	18
Histological subtype			
Epithelioid mesothelioma	6	10	16
Sarcomatoid mesothelioma	0	5	5
Biphasic mesothelioma	0	4	4
Other	0	0	0
Asbestos exposure			
Had no exposure	2	3	5
Had exposure	4	16	20
Stage of disease			
Ia	0	0	0
Ib	0	1	1
II	0	1	1
III	1	1	2
IV	5	16	21

Level 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2
Level −1: pemetrexed 500 mg/m^2 + cisplatin 60 mg/m^2
SD, standard deviation.

Dose-Escalation, Dose-Limiting Toxicity and RD

One patient in Level 1 of Step 1 died on Day 14 of Cycle 1 due to exacerbation of pneumonia, respiratory failure (hypoxia) and disseminated intravascular coagulation (DIC). The ESEC evaluated the case of the early death. Since the patient had had the shadow of the lung detected by radiographic image prior to receiving study treatment, it was unlikely that the administration of pemetrexed was the primary cause of the pneumonia. The autopsy of this patient showed that interstitial changes in the lung were mild and the pathological diagnosis was an organizing pneumonia. The result of the autopsy was compatible with the clinical course and suggested that the direct cause of the death was not the drug-induced interstitial pneumonia but the exacerbation of infectious pneumonia, worsened by the study treatment. The case, therefore, was considered not appropriate for the DLT evaluation.

One patient was added in this dose level to assess the safety profile additionally. Among the six patients in Level 1 excluding the case inappropriate for the DLT evaluation, two patients showed DLTs: drug-induced pneumonitis in one patient and dose delay of Cycle 2 initiation due to decreased neutrophil count in the other. According to the protocol definition, Level 1 was determined to be an RD for the next phase (Fig. 1).

The ESEC, however, recommended examining the treatment at Level −1 (pemetrexed 500 mg/m^2 and cisplatin 60 mg/m^2) exploratively to accumulate more safety information. Accordingly, six patients were enrolled and treated at Level −1, and no DLTs were observed in this dose level.

Evaluating the data of these two levels together, the ESEC agreed to continue Step 2 carefully with the dose of Level 1. The sponsor decided to carry forward into Step 2 with

an RD of Level 1 (pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2). In Step 2, 12 patients were treated at Level 1.

Efficacy

Nineteen patients (7 in Step 1 and 12 in Step 2) in Level 1 were included in the efficacy analysis set and of 19 patients, seven patients had PR, five patients had stable disease (SD), six patients had PD and one patient was classified as not evaluated. An overall response rate (ORR) was 36.8% [95% confidence interval (CI): 16.3%–61.6%]. The 95% one-sided confidence lower limit was 18.8%, exceeding the threshold level of 10%. The six patients in Level −1 had PR; thus, the ORR for all 25 patients treated with the study drug reached 52.0% (13 total PR, 95% CI: 31.3%–72.2%).

The secondary efficacy variables were time-to-event outcomes (the duration of response, PFS and overall survival time), 1-year survival rate, QOL and pulmonary function test. The median duration of response was 5.2 months (95% CI: 4.3–7.3 months) for the seven responders in the efficacy analysis set (Table 2). The median duration of response for the six responders at Level −1 was again 5.2 months. For the efficacy analysis set, median PFS was 4.7 months (95% CI: 1.3–6.5 months) and MST was 7.3 months (95% CI: 4.6–14.2 months, Fig. 2) with 1-year survival rate of 36.8% (95% CI: 15.2%–58.5%). Median PFS for the six patients at Level −1 was 10.1 months. MST at Level −1 could not be calculated by Kaplan–Meier method. The 1-year survival rate of Level −1 (66.7%) was beyond 50%.

The QOL-ACD and FACT-L measures were used for QOL evaluation. There were no major changes from prior to Cycle 1 to 3 months after Cycle 1 treatment in the mean scores for the activity and physical condition subscales of QOL-ACD (Table 3); however, mean scores from prior to Cycle 1 to 3 months after Cycle 1 treatment for the psychological condition and social relationships subscales numerically increased. The mean LCS score of FACT-L did not change substantially from prior to Cycle 1 to 3 months after Cycle 1 treatment (data not shown). These score changes indicate that QOL of the patients was maintained without worsening from baseline. Pulmonary function was also maintained with no worsening from baseline observed in the pulmonary function tests (FEV_1, FVC and VC) in the efficacy analysis set (data not shown).

Safety

Of 25 patients of the safety analysis set, three died during the study period: one (Level 1, Step 1) from exacerbation of pneumonia as a pre-existing complication, respiratory failure, and DIC, as described earlier, and the other two (Step 2) due to study disease. Two patients experienced non-fatal serious adverse events (fever and aspiration pneumonia, respectively). A causal relationship between fever and the study drugs could not be ruled out, but the aspiration pneumonia was not considered related to study drugs. Adverse events leading to discontinuation from study treatment were observed in six patients: one patient at Level 1 and three patients at Level −1 in Step 1 and in two patients in Step 2. Adverse event leading to discontinuation in two or more patients was increased blood creatinine (two patients).

Table 2. Summary of time-to-event outcomes and 1-year survival rates

	Step 1 Level −1 ($n = 6$)	Level 1 ($n = 19$)	All treated ($n = 25$)
Duration of response (months)			
Responders	6	7	13
Med	5.2	5.2	5.2
(95% CI)	3.1 − *	4.3–7.3	4.3–7.3
Range	2.7–9.6	2.0–7.3	2.0–9.6
Censored (%)	50	14.3	30.8
Progression free survival (months)			
Med	10.1	4.7	4.8
(95% CI)	4.3 − *	1.3–6.5	2.5–7.1
Range	3.3–12.1	0.5–9.6	0.5–12.1
Censored (%)	50	10.5	20
Overall survival (months)			
Med	NA	7.3	9.2
(95% CI)	11.1 − *	4.6–14.2	5.8–14.4
Range	8.6–19.3	0.5–21.5	0.5–21.5
Censored (%)	66.7	21.1	32
1-year survival rate (%)			
	66.7	36.8	44.0
(95% CI)	28.9–100.0	15.2–58.5	24.5–63.5

*Not calculated. NA, not assessed.
Level 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2.
Level −1: pemetrexed 500 mg/m^2 + cisplatin 60 mg/m^2.
CI, confidence interval.

Grade 3 or more laboratory TEAEs were observed in 16 patients: four patients at Level 1 and five patients at Level −1 in Step 1 and in seven patients in Step 2. Laboratory TEAEs observed in at least half of the 25 patients were decreased-hemoglobin, decreased red blood cell count, decreased neutrophil count, decreased white blood cell count, decreased lymphocyte count, increased blood urea and decreased body weight (Table 4). Grade 3 or more non-laboratory TEAEs were observed in eight patients: three patients at Level 1 and one patient at Level −1 in Step 1 and in four patients in Step 2. Non-laboratory TEAEs observed in at least half of the 25 patients were nausea, anorexia, vomiting and malaise. No major differences between Levels 1 and −1 (Step 1) in the incidence of TEAEs were noted.

For the 19 patients at Level 1, laboratory TEAEs of grade 3 or higher, possibly related to drug, and observed in at least two patients were decreased neutrophil count (seven patients, 36.8%), decreased hemoglobin (six patients, 31.6%), decreased white blood cell count (five patients, 26.3%), decreased lymphocyte count (five patients, 26.3%),

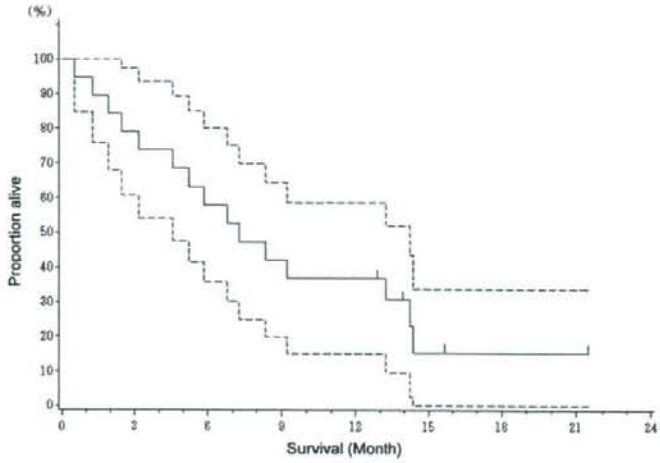

Figure 2. Kaplan–Meier plot of overall survival in the efficacy analysis set. Solid lines, overall survival; dotted lines, high and low limits of 95% confidence interval.

decreased platelet count (two patients, 10.5%) and decreased blood potassium (two patients, 10.5%). Non-laboratory adverse drug reactions of grade 3 or higher observed in at least two patients were vomiting (three patients, 15.8%), anorexia (three patients, 15.8%), nausea (two patients, 10.5%) and malaise (two patients, 10.5%). Adverse drug reactions of grade 3 or higher for the six patients in Level −1 were decreased neutrophil count (three patients), decreased-hemoglobin (two patients), decreased lymphocyte count (two patients) and decreased red blood cell count (one patient).

DISCUSSION

This Phase I/II study reports the first experience of the combination of pemetrexed and cisplatin therapy in Japanese patients. The RD of Pem/Cis combination therapy was established at pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, with pemetrexed administration on Day 1 of each 21-day cycle followed by cisplatin, which is the same regimen used in worldwide for patients with MPM (16).

Of the 19 patients evaluable for efficacy at the RD level, there were PRs in seven patients, for an ORR of 36.8% (95% CI: 16.3%–61.6%). A pivotal Phase III study of the same regimen as that applied of the present study, yielded a response rate of 41.3% (95% CI: 34.8%–48.1%) in 225 patients (16). The response rates from both studies are comparable despite of the large difference in sample size.

The response rate of all the 25 treated patients was higher than the response rate for the 19 patients treated at the RD (52.0% versus 36.8%). This is due to the fact that all the six patients in Level −1 had PR. The excellent outcome observed in Level −1 may be attributed to differences between those patients who received the RD and those patients in Level −1 in the histological subtype of mesothelioma. All six patients in Level −1 had an epithelial subtype, which is known as a favorable prognostic factor, while only about half of the 19 patients at the RD had this subtype. In addition, the PS of the patients in Level −1 was better than the patients at RD.

A secondary efficacy endpoint MST showed 7.3 months in this study, shorter than that of the Pem/Cis arm in the Phase III study (12.1 months) (16). Although it would be difficult to compare MST of this study derived from a small sample size with the large Phase III study ($n = 226$), the discrepancy of survival between the two studies could be ascribed for the demographic characteristics of patients in both. There are less patients who had good prognostic factors in this study than in the Pem/Cis arm of the Phase III study: epithelial subtype: 52.6% versus 68.1%, a good PS: 21.1% (PS = 0) versus 51.8% (Karnofsky PS = 90/100) and clinical stage I/II: 8.0% versus 22.6% (16).

In this study, the most common adverse events (>50% of patients) were decreased-hemoglobin, erythropenia, neutropenia, leukopenia and lymphopenia for laboratory parameters, and nausea, anorexia, and vomiting for non-laboratory parameters. These hematologic and gastrointestinal events were similarly observed in the Pem/Cis arm of the pivotal Phase III study (16). No grade 3/4 febrile neutropenia toxicity which is a potentially life-threatening event was reported in our study. One death by pneumonitis was observed in this study; however, the patient was considered to have a pre-existing condition before initial treatment with study therapy. Adverse events observed in this study were predictable from safety profile observed in overseas trials and market experiences of pemetrexed and cisplatin combination therapy.

Table 3. Summary of QOL questionnaire for cancer patients treated with anticancer drugs (Level 1, $n = 19$)

Subscale	Measurement Point	n	Mean	SD	Min	Med	Max
Activity							
	Prior to Cycle1	19	62.9	25.35	20.0	60.0	100.0
	Prior to Cycle2	15	61.8	32.27	5.0	70.0	100.0
	Prior to Cycle3	14	69.6	21.79	20.0	75.0	95.0
	Cycle1 + 3M	11	60.5	32.13	5.0	70.0	100.0
Physical							
	Prior to Cycle1	19	64.7	22.33	15.0	70.0	100.0
	Prior to Cycle2	15	64.3	18.11	20.0	65.0	95.0
	Prior to Cycle3	14	66.2	18.33	30.0	70.0	85.0
	Cycle1 + 3M	11	61.4	21.46	35.0	60.0	95.0
Psychological							
	Prior to Cycle1	19	53.2	20.62	12.5	56.3	81.3
	Prior to Cycle2	15	59.6	24.87	12.5	62.5	100.0
	Prior to Cycle3	14	58.0	17.41	31.3	56.3	87.5
	Cycle1 + 3M	11	61.4	18.07	37.5	68.8	87.5
Social							
	Prior to Cycle1	19	32.9	21.56	5.0	25.0	75.0
	Prior to Cycle2	15	33.7	19.13	0.0	25.0	70.0
	Prior to Cycle3	14	43.6	19.94	10.0	42.5	85.0
	Cycle1 + 3M	11	36.4	22.59	10.0	30.0	85.0
Face scale							
	Prior to Cycle1	19	50.0	23.57	0.0	50.0	100.0
	Prior to Cycle2	14	55.4	24.37	0.0	50.0	100.0
	Prior to Cycle3	14	64.3	23.44	25.0	50.0	100.0
	Cycle1 + 3M	11	63.6	20.50	25.0	75.0	100.0

Level 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2. M, months. QOL, quality of life.

CONCLUSION

The RDs for the Pem/Cis combination are pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, which is the same regimen used in worldwide for patients with MPM. The combination shows promising efficacy with an acceptable safety profile in Japanese patients with MPM.

On January 2007, Pem/Cis combination therapy was approved and launched for the treatment of patients with MPM in Japan. Intensive post-marketing surveillance in patients with MPM is ongoing.

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Conflict of interest statement

S.A. and Y.N. are employed by the sponsor, Eli Lilly Japan K.K.; N.S. and M.F. are paid consultants to the sponsor.

Table 4. Summary of treatment-emergent adverse events (TEAEs) reported >25% patients

System organ class preferred term	Step 1 Level −1 ($n = 6$)	Level 1 ($n = 19$)	All treated ($n = 25$)
Patients with ≥1 TEAEs	6	19	25
Laboratory			
Hemoglobin decreased	6	18	24
Red blood cell count decreased	6	16	22
Neutrophil count decreased	5	16	21
White blood cell count decreased	5	15	20
Lymphocyte count decreased	5	12	17
Blood urea increased	5	11	16
Weight decreased	3	12	15
Blood albumin decreased	2	10	12
Platelet count decreased	4	8	12
Protein total decreased	3	9	12
Blood creatinine increased	4	7	11
Neutrophil count increased	2	8	10
White blood cell count increased	2	8	10
Blood sodium decreased	2	7	9
Alanine aminotransferase increased	1	7	8
Protein urine present	1	7	8
Aspartate aminotransferase increased	1	6	7
Blood magnesium decreased	2	5	7
Blood potassium decreased	0	7	7
Non-laboratory			
Nausea	6	18	24
Anorexia	6	16	22
Vomiting	3	15	18
Malaise	5	10	15
Constipation	3	9	12
Hiccups	3	5	8
Rash	2	6	8
Diarrhoea	1	6	7
Oedema	2	5	7
Pyrexia	2	5	7
Dysgeusia	3	4	7
Headache	1	6	7

Level 1: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2
Level −1: pemetrexed 500 mg/m^2 + cisplatin 60 mg/m^2
MedDRA Ver 9.0.

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