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
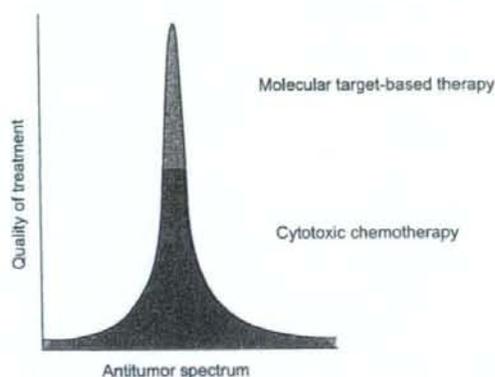

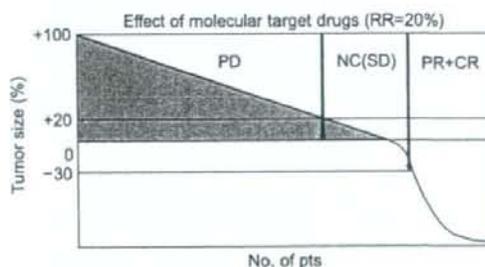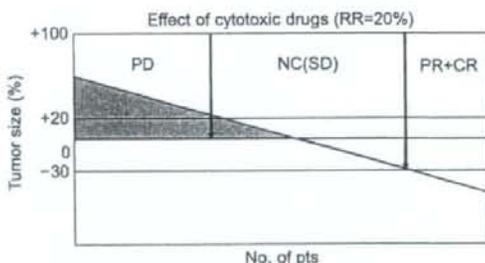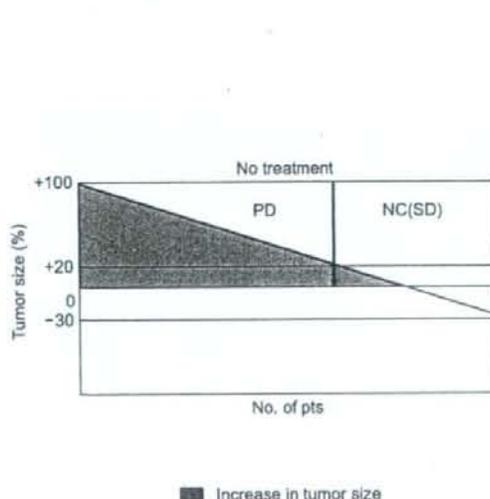Fig. 1. Improvement of treatment quality.

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. 2. Difference in the effect of cytotoxic drugs and molecular target drugs (waterfall plots).
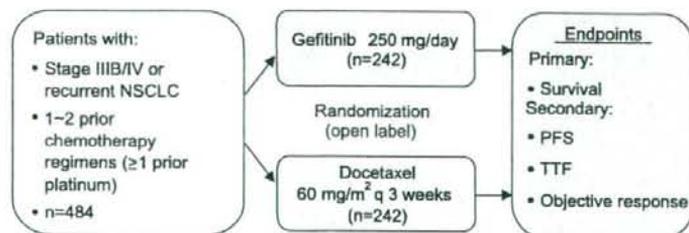
with docetaxel(26), but non-inferiority could not be demonstrated, and survival time at each time point assessed in the gefitinib group was slightly poorer than in the docetaxel group at each time point during early phase after the beginning of treatment (Table 3, Fig. 3, 4). Waterfall plots are being 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.

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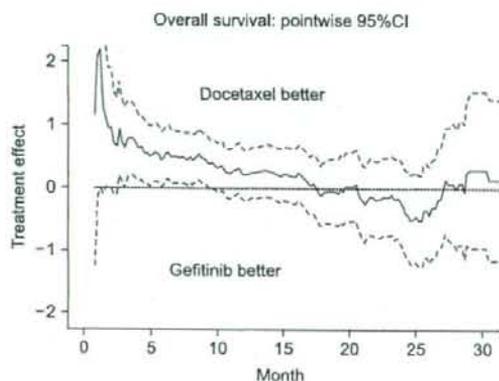
Fig. 4. Treatment effect at each time point. Analysed by Prof. Masahiro Takeuchi, Kitasato University, Division of Biostatistics & Division of Pharmaceutical Medicine. Courtesy of Prof. M. Takeuchi, Kitasato University.

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.

■ 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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Clinical Outcome of Chemoradiation Therapy in Patients with Limited-Disease Small Cell Lung Cancer with Ipsilateral Pleural Effusion

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Background: The indications for definitive thoracic radiotherapy (TRT) in limited-disease small cell lung cancer (LD-SCLC) and ipsilateral pleural effusion have not been thoroughly investigated. We retrospectively investigated the clinical outcome of LD-SCLC patients with ipsilateral pleural effusion.

Methods: The medical records of SCLC patients who received treatment at the National Cancer Center Hospital East between July 1992 and December 2006 were reviewed. Sixty-three of the 373 LD-SCLC patients (17%) had ipsilateral pleural effusion. Of these, 62 patients received chemotherapy as an initial treatment, and were included in this study. Since about 1998, definitive TRT was routinely performed if the patient's pleural effusion disappeared after induction chemotherapy. The 62 patients were divided into three subgroups: group A included patients who received chemotherapy and TRT ($n = 26$), group B included patients who did not receive TRT in spite of the disappearance of pleural effusion after first-line chemotherapy ($n = 8$), and group C included patients who did not receive TRT and whose pleural effusion persisted after first-line chemotherapy ($n = 28$).

Results: The response rate for first-line chemotherapy was 74%. Ipsilateral pleural effusion disappeared after first-line chemotherapy in 34 patients (55%). The median overall survival time was 11.8 months, and the 2 and 3-year survival rates were 21 and 10%, respectively. In groups A, B, and C, the median survival times were 19.2, 10.5, and 9.2 months, respectively, and the 2-year survival rates were 38, 25, and 7%, respectively.

Conclusion: Long-term survival was achieved by LD-SCLC patients with ipsilateral pleural effusion who successfully underwent chemoradiotherapy.

L ung cancer is the leading cause of cancer-related deaths worldwide. In Japan, over 56,000 people died of lung cancer in 2003. Small cell lung cancer (SCLC) accounts for about 15% of all forms of lung cancer. SCLC has a more aggressive biologic behavior than non-small cell lung cancer. At the time of presentation, two-thirds of patients exhibit disseminated disease. SCLC is sensitive to chemotherapy, with a response rate of 70 to 80%. A clinical two-stage system proposed by the Veterans Administration Lung Study Group distinguishes limited-disease (LD) and extensive-disease (ED) in SCLC.[1] LD is defined as being limited to one hemithorax, including mediastinal, contralateral hilar, and ipsilateral supraclavicular lymph nodes, whereas ED represents tumor spread beyond these regions. The current standard care for LD-SCLC is a combination of chemotherapy and thoracic radiotherapy (TRT). On the other hand, ED-SCLC is treated with chemotherapy alone. The original definition of LD was a tumor volume that could be encompassed by a reasonable radiotherapy plan. According to the International Association for the Study of Lung Cancer (IASLC)'s consensus report, on the other hand, the classification of LD-SCLC includes bilateral hilar and/or supraclavicular nodal involvement and ipsilateral pleural effusion.[2] However, the indication for definitive TRT in patients with LD-SCLC and ipsilateral pleural effusion have not been thoroughly investigated. Recently, the IASLC proposed the seventh edition of the tumor, node, metastasis (TNM) classification for lung cancer. In the proposals, the presence of a pleural effusion is considered as M1 disease.[3–6]

Definitive TRT is contraindicated in lung cancer patients with malignant pleural effusion. We have sometimes treated SCLC cases in which the ipsilateral pleural effusion disappeared after induction chemotherapy. Should definitive TRT be indicated in SCLC patients if the ipsilateral pleural effusion disappears after induction chemotherapy? Since about 1998, we have routinely performed definitive TRT if the patient's pleural effusion disappeared after induction chemotherapy. In this retrospective study, we investigated the clinical course and outcome of LD-SCLC patients with ipsilateral pleural effusion and exam-

ined the overall survival in patients who received chemotherapy and TRT, comparing with that of ED-SCLC or LD-SCLC patients without ipsilateral pleural effusion. We also applied the proposed seventh edition of the TNM stage to our cohort.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of lung cancer patients who received treatment at the National Cancer Center Hospital East between July 1992 and December 2006. During this period 699 patients were newly diagnosed as having SCLC. Three-hundred and seventy-three patients were diagnosed as having LD-SCLC, and 326 were diagnosed as having ED-SCLC using conventional staging procedures, including a medical history and physical examination, chest radiography, computed tomography (CT) scan of the chest, CT scan or ultrasound of the abdomen, bone scan, and CT scan or magnetic resonance imaging of the brain. In this study, LD-SCLC was defined as disease limited to one hemithorax, including mediastinal, contralateral hilar, and supraclavicular lymph nodes, ipsilateral pleural effusion, and pericardial effusion; ED-SCLC was defined as tumor spread beyond these manifestations.[2] Sixty-three of the 373 LD-SCLC patients (17, 95% confidence interval (CI): 13–21%) had ipsilateral pleural effusion. Thirty-seven SCLC patients underwent surgical resection as an initial treatment, and 13 patients received only TRT and/or best supportive care. Remaining 649 patients received chemotherapy as an initial treatment. Of these, 62 LD-SCLC patients had ipsilateral pleural effusion, and were included in this study. The patient characteristics are shown in Table 1. The breadth of the pleural effusion was measured using a CT scan of the chest (Figure 1). Cytologic examination of the pleural effusion prior to treatment was performed in 26 patients. Eleven patients had cytologically positive effusion. Ten patients also had pericardial effusion. Three patients had solid pleural tumor and pleural effusion detected on CT scan. Twenty-six patients had atelectasis. Of these, 14 patients received cytologic examination of the pleural effusion, and four patients had cytologically positive effusion.

We collected clinical data on the patients from their medical records; this data included the chemotherapy regimen that was received, the response to first-line chemotherapy, whether pleural effusion disappeared after first-line chemotherapy, and whether the patient underwent definitive TRT. The World Health Organization's response criteria were used.[7]

Overall survival was defined as the interval between the start of treatment and death or the final follow-up visit. Median overall survival was estimated using the Kaplan-Meier analysis method.[8] Survival data was compared among groups using a log-rank test. The breadth of pleural effusion was compared using the Mann-Whitney U test. All reported p values are two-sided.

RESULTS

The induction chemotherapy regimens were shown in Table 2. Most common regimen was cisplatin or carboplatin plus etoposide. In LD patients with ipsilateral pleural effusion, there were three complete responses, 43 partial re-

sponses, seven no changes, and six progressive diseases. Response was not evaluated in three patients because of early death. The response rate was 74% (95% CI: 62–84%). Ipsilateral pleural effusion disappeared after first-line chemotherapy in 34 patients (55, 95% CI: 42–68%).

TABLE 1. Patient Characteristics

	LD-SCLC without Ipsilateral Pleural Effusion	LD-SCLC with Ipsilateral Pleural Effusion	ED-SCLC
No. of patients	270	62	317
Sex			
Male	226	50	262
Female	44	12	55
Age, yr			
Median	66	67	66
Range	38–87	46–79	28–85
Performance status			
0	71	2	20
1	178	45	203
2	14	10	59
3	6	5	28
4	1	0	7
Breadth of pleural effusion on CT scan, cm			
Median		2.3	
Range		0.5–9.4	
Cytology of pleural effusion			
Positive		11	
Negative		15	
Not examined		36	

Patients who received chemotherapy as an initial treatment were included.
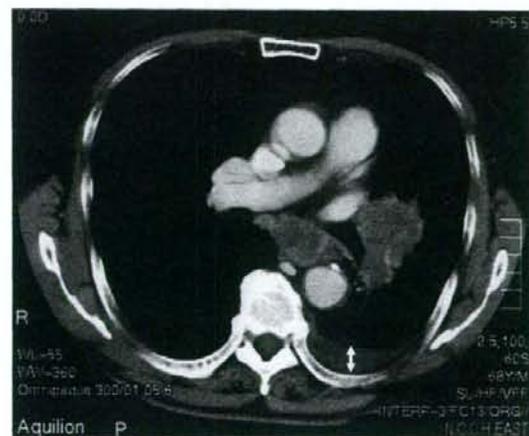LD, limited-disease; SCLC, small cell lung cancer; ED, extensive-disease; CT, computed tomography.

FIGURE 1. Ipsilateral pleural effusion. The arrow indicates the breadth of pleural effusion.

TABLE 2. Induction Chemotherapy Regimens and Response

	LD-SCLC without Ipsilateral Pleural Effusion	LD-SCLC with Ipsilateral Pleural Effusion	ED-SCLC
Chemotherapy regimens			
Platinum + ETP	252	54	154
Cisplatin and irinotecan containing regimens	10	2	92*
CODE	7	5	52
CAV/PE	1	1	11
Other	0	0	8
Response			
CR	64	3	28
PR	189	43	213
NC	8	7	37
PD	5	6	18
NE	4	3	21
Response rate (%) (95% CI)	94 (90–96)	74 (62–84)	76 (71–81)

*Nine patients received chemotherapy of cisplatin and topotecan.

LD, limited-disease; SCLC, small cell lung cancer; ED, extensive-disease; ETP, etoposide; CODE, weekly cisplatin, vincristine, doxorubicin, plus etoposide; CAV/PE, cyclophosphamide, doxorubicin, plus etoposide alternating with cisplatin plus etoposide; CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable; CI, confidence interval.

Since about 1998, definitive TRT to the primary lesion and mediastinum was routinely performed in patients whose pleural effusion disappeared after chemotherapy. We divided the 62 patients in this study into three subgroups: group A included patients who received chemotherapy and TRT ($n = 26$), group B included patients who did not receive TRT in
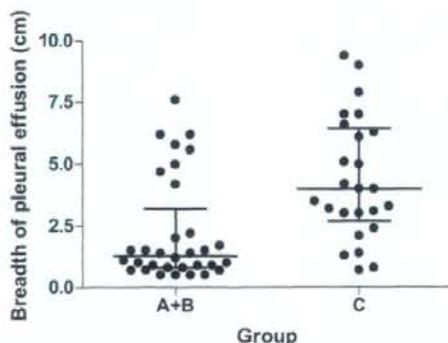
FIGURE 2. Breadth of pleural effusion in subgroup A + B, and C. Group A included patients who underwent chemotherapy and thoracic radiotherapy (TRT) ($n = 26$), group B included patients who did not undergo TRT in spite of the disappearance of pleural effusion after first-line chemotherapy ($n = 8$), and group C included patients who did not undergo TRT and whose pleural effusion persisted after first-line chemotherapy ($n = 28$). The line represents the median with the interquartile range.

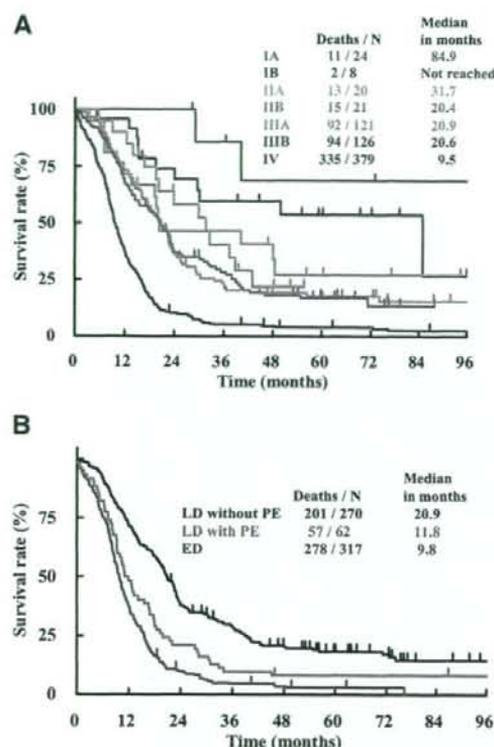spite of the disappearance of pleural effusion after first-line chemotherapy ($n = 8$), and group C included patients who did not receive TRT and whose pleural effusion persisted after first-line chemotherapy ($n = 28$).

The median (range) breadth of pleural effusion was 11.2 cm (0.5–7.6 cm) in group A, 1.8 cm (0.5–5 cm) in group B, and 4 cm (0.7–9 cm) in group C. Combining group A and B, the median breadth of pleural effusion was 1.3 cm, which was significantly lower than that of group C ($p = 0.0007$) (Figure 2).

In group A, all but two patients received platinum-based chemotherapy. One patient received weekly cisplatin, vincristine, doxorubicin, plus etoposide (PE) therapy, and the other patient received cyclophosphamide, doxorubicin, PE alternating with cisplatin PE therapy. Three of the 26 patients in group A underwent TRT (twice daily, 45 Gy in total) concurrently with the first course of chemotherapy. The breadths of pleural effusion in those three patients were 0.7, 0.8, and 1.0 cm. Two, seven, and one patient underwent TRT (once daily, 50 Gy in total) concurrently with the second, third, and fourth courses of chemotherapy, respectively. Thirteen patients underwent TRT (once daily, 50 Gy in total) sequentially after chemotherapy. Six patients received prophylactic cranial irradiation (PCI) of 25 Gy.

Figure 3*A* showed the survival of the all 699 SCLC patients by the proposed seventh edition of TNM stage. Figure 3*B* showed the survival of the 649 SCLC patients who received chemotherapy as an initial treatment. The survival of LD patients with ipsilateral pleural effusion was intermediate between those of LD patients without effusion and ED patients ($p < 0.0001$). The median survival time in LD patients with ipsilateral pleural effusion was 11.8 months (95% CI: 9.2–16.6), and the 1, 2, 3 and 5-year survival rates were 48, 21, 10 and 8%, respectively. Four patients have survived for over 5 years. One patient had a cytologically negative pleural effusion, and cytologic examinations were not performed for the remaining three patients. Breadth of pleural effusion of these four patients ranged from 1.0 to 1.5 cm. Two of these four patients have not shown any progression for more than 5 years. One patient who received only chemotherapy as an initial treatment developed a local recurrence 3 years after the first-line treatment. This patient received concurrent chemoradiotherapy and achieved a complete response. Unfortunately, he developed brain metastasis 9 years after the first-line chemotherapy and received whole brain radiotherapy. The other patient developed cervicular and inguinal node metastases 8 months after the initiation of first-line chemotherapy and concurrent TRT with three courses of chemotherapy. This patient received second, third, and fourth-line chemotherapy, radiotherapy to the cervicular and inguinal node metastases, and surgical resection of the recurrent inguinal node metastasis. He has not shown any signs of progression for 3 years and 3 months after the final surgical resection of the metastatic inguinal node. All three patients who had solid pleural tumor died within 31 months.

Survival analyses for the subgroups in LD patients with ipsilateral pleural effusion are shown in Figures 4, 5 and Table 3. In group A, the median survival time was 19.2 months (95% CI: 16.7–27.9) and the 1 and 2-year survival rates were 81 and
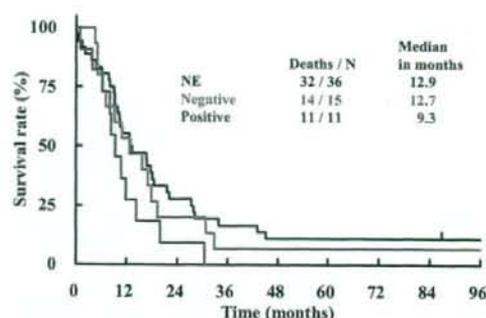
A

	Deaths / N	Median in months
IA	11 / 24	84.9
IB	2 / 8	Not reached
IIA	13 / 20	31.7
IIB	15 / 21	20.4
IIIA	92 / 121	20.9
IIIB	94 / 126	20.6
IV	335 / 379	9.5

FIGURE 5. Overall survival according to the results of cytologic examination for ipsilateral pleural effusion. NE, not examined.

	Deaths / N	Median in months
NE	32 / 36	12.9
Negative	14 / 15	12.7
Positive	11 / 11	9.3

B

	Deaths / N	Median in months
LD without PE	201 / 270	20.9
LD with PE	57 / 62	11.8
ED	278 / 317	9.8

FIGURE 3. A, Overall survival in the all 699 patients with small cell lung cancer by the proposed seventh edition of the tumor, node, metastasis stage. B, Overall survival in the 649 patients who received chemotherapy as an initial treatment. LD, limited-disease; SCLC, small cell lung cancer; ED, extensive-disease.

	Deaths / N	Median in months
A	22 / 26	19.2
B	7 / 8	10.5
C	28 / 28	9.2
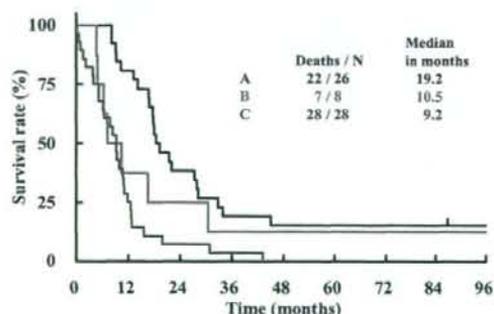
FIGURE 4. Overall survival in subgroups A, B, and C.

38%, respectively. The median survival time of patients with cytologically positive and negative pleural effusion were 9.3 months (95% CI: 3.8–14.2) and 12.7 months (95% CI: 5.1–17.9), respectively. The median survival time of those patients

whose pleural effusions were not examined cytologically was 12.9 months (95% CI: 9.2–18.4). This difference was not statistically significant ($p = 0.1959$).

Disease progression was confirmed in 21 of the 26 patients in group A. The sites of first disease progression included the brain ($n = 10$), regional lymph nodes ($n = 5$), primary lesion ($n = 3$), distal lymph nodes ($n = 2$), liver ($n = 1$), adrenal gland ($n = 1$), and bone ($n = 1$). Twelve (57%) were distant, seven (33%) were local-regional, and two (10%) were both local-regional and distant. Brain metastasis was the only site of recurrence in nine patients. These nine patients had not received PCI. At the time of disease progression, ipsilateral pleural effusion recurred in 10 of the 18 patients.

DISCUSSION

LD-SCLC with ipsilateral pleural effusion accounted for 9% of all the patients with SCLC (63 of 669 patients) and 17% of all the patients with LD-SCLC (63 of 373 patients). Twenty-six (41%) of the LD-SCLC patients with ipsilateral pleural effusion received chemotherapy and definitive TRT. The median survival time of these patients was 19.2 months (95% CI: 16.7–27.9), and the 1 and 2-year survival rates were 81 and 38%, respectively. This overall survival time was comparable to that of LD patients without ipsilateral pleural effusion.

Among the LD-SCLC patients with ipsilateral pleural effusion, the median survival time was 11.8 months (95% CI: 9.2–16.6), and the 1 and 2-year survival rates were 48 and 21%, respectively. This survival was intermediate between those of LD patients without ipsilateral pleural effusion and ED patients. An analysis of 2,580 patients treated in the Southwest Oncology Group trials demonstrated that the survival of patients with LD-SCLC and ipsilateral pleural effusion was not significantly different from that of patients with ED-SCLC and a single metastatic lesion. The median survival times were 13.0 and 12.0 months ($p = 0.85$), respectively.[9] Thus, our data was compatible with that of the Southwest Oncology Group trials. Another analysis of 5,758 patients with SCLC from the IASLC database also demonstrated consistent results.[10]

According to the proposed seventh edition of the TNM classification for lung cancer, LD patients with ipsilateral

TABLE 3. Survival Data

Subgroup	No. of Patients	Median Survival Time (mo) (95%CI)	1-yr Survival Rate (%)	2-yr Survival Rate (%)	3-yr Survival Rate (%)
ED	317	9.8 (8.8–10.6)	37	10	4
LD without ipsilateral pleural effusion	270	20.9 (19.1–22.7)	72	38	29
LD with ipsilateral pleural effusion	62	11.8 (9.2–16.6)	48	21	10
Receiving TRT	26	19.2 (16.7–27.9)	81	38	19
Not receiving TRT	36	9.1 (6.0–10.8)	28	11	6
Not receiving TRT in spite of disappearance of pleural effusion	8	10.5 (4.5–30.6)	38	25	13
Not receiving TRT and persistent pleural effusion after chemotherapy	28	9.2 (5.1–10.8)	25	7	4
Cytologically positive pleural effusion	11	9.3 (3.8–14.2)	27	9	0
Cytologically negative pleural effusion	15	12.7 (5.1–17.9)	53	20	7
Without cytological examination	36	12.9 (9.2–18.4)	56	28	17

CI, confidence interval; ED, extensive-disease; SCLC, small cell lung cancer; LD, limited-disease; TRT, thoracic radiotherapy.

pleural effusion will be classified as stage IV.[3–6] However, prognosis of LD patients with ipsilateral effusion is better than that of ED patients with distant metastasis. If surgical cases such as clinical stage I cases were excluded, the simple staging system, LD or ED, seemed to be sufficient to select treatment strategy.

In our study, four LD patients with ipsilateral pleural effusion have survived for more than 5 years. Three patients received chemotherapy and TRT as an initial treatment. The remaining one patient received only chemotherapy as an initial treatment but received chemotherapy and TRT after a local recurrence. TRT probably contributed to local control and long-term survival in those LD-SCLC patients with ipsilateral pleural effusion. A previous systematic review demonstrated that an early timing of TRT contributed to a significant improvement in long-term survival, compared with a late timing.[11] In patients whose ipsilateral pleural effusion disappears after chemotherapy, definitive TRT should be considered as early as possible.

Disease progression was confirmed in 21 out 26 patients (81%) who received chemotherapy and definitive TRT. The most common site of first failure was the brain. Nine of the 10 patients had not received PCI. In these nine patients, brain metastasis was the only site of recurrence. In LD-SCLC patients with ipsilateral pleural effusion who undergo chemotherapy and definitive TRT, PCI may further improve treatment outcome.

Cytologic examinations of the pleural effusion before treatment were only performed in 26 patients (42%). These cytologic results did not significantly affect overall survival. However, all nine patients with cytologically positive pleural effusion died within 31 months. A similar observation was reported in a cohort of IASLC database.[10]

Chemotherapy regimens were heterogeneous between LD and ED patients. More patients with ED received cisplatin and irinotecan containing regimens. However, response rates were similar between LD with ipsilateral pleural effusion and ED patients (74 and 76%).

In conclusion, long-term survival was achieved by LD-SCLC patients who underwent definitive TRT after their ipsilateral pleural effusion disappeared after induction chemotherapy. A prospective randomized trial is warranted to compare chemotherapy alone with chemoradiotherapy in LD-SCLC patients with ipsilateral pleural effusion. This work was supported in part by a Grant from the Ministry of Health, Labor, and Welfare for the 3rd term Comprehensive Strategy for Cancer Control and a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor, and Welfare, Japan.

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Performance Status and Sensitivity to First-line Chemotherapy Are Significant Prognostic Factors in Patients With Recurrent Small Cell Lung Cancer Receiving Second-line Chemotherapy

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BACKGROUND. To the authors' knowledge, the prognostic factors in recurrent small cell lung cancer (SCLC) patients treated with second-line chemotherapy have not yet been clearly identified to date.

METHODS. Between July 1992 and December 2003, 232 of 515 patients who were diagnosed to have SCLC at the National Cancer Center Hospital East were administered second-line chemotherapy for recurrent disease. The authors retrospectively analyzed the relation between clinical factors evaluated at the time of recurrence and the response to second-line chemotherapy or survival in these patients.

RESULTS. The results of univariate analyses revealed that response was significantly associated with the performance status (PS) alone, whereas survival was significantly associated with the PS, disease extent, and sensitivity to first-line chemotherapy. Multivariate analysis identified PS ($P < .0001$) and sensitivity to first-line chemotherapy ($P = .0024$) as the independent prognostic factors for survival. When the patients were grouped according to these 2 significant prognostic factors, the survival of patients with a PS of 0 to 1 was significantly better than that of the patients with a PS of 2 to 4 both among cases that were sensitive and those that were refractory to first-line chemotherapy. Although the survival of sensitive recurrent cases was significantly better than that of the refractory recurrent cases among the patients with a PS of 0 to 1 patients, no survival difference was observed between the sensitive and refractory recurrent cases in the patients with a PS of 2 to 4.

CONCLUSIONS. Both PS and sensitivity to initial chemotherapy were found to be significant prognostic factors for survival in recurrent SCLC patients treated with second-line chemotherapy. These 2 factors should therefore be used as stratification factors in future clinical trials. *Cancer* 2008;113:2518–23. © 2008 American Cancer Society.

KEYWORDS: small cell lung cancer, second-line chemotherapy, prognostic factor, performance status, sensitive recurrence, refractory recurrence.

Although the proportion of small cell lung cancer (SCLC) among cases of lung cancer has been decreasing in recent years, it still accounts for 14% of all new lung cancer cases, and the actual number of patients was estimated to be 77,000 in the US and Europe in 2004.[1] In general, SCLC is an exceedingly aggressive cancer, and greater than 66% of patients have clinically obvious metastatic disease at the time of diagnosis.[2] SCLC is also extremely sensitive to chemotherapy; therefore, the main treatment strategy for SCLC is

systemic chemotherapy. Currently, both cisplatin plus etoposide (PE) and cisplatin plus irinotecan (IP) are considered as standard chemotherapeutic regimens for SCLC.[3,4] Despite the high initial sensitivity to chemotherapy, the majority of patients develop disease recurrence. The prognosis of patients with recurrent SCLC is usually abysmal, and the overall survival time after recurrence is reportedly 2 to 4 months.[5]

In general, second-line chemotherapy is considered for cases with recurrent SCLC, and a few studies have reported on the efficacy of some second-line treatments.[6,7] For example, a prospective randomized trial comparing oral topotecan with best supportive care (BSC) revealed the benefits of treatment with oral topotecan in terms of the survival and quality of life.[7]

Although some studies have shown the importance of both response and the duration of the response to initial chemotherapy in predicting the efficacy of second-line chemotherapy,[8-10] the number of studies conducted to identify the prognostic factors in recurrent SCLC patients is quite limited. In this retrospective study, we investigated the prognostic factors in recurrent SCLC patients administered second-line chemotherapy to determine the factors that need to be used for stratifying the patients in future clinical trials.

MATERIALS AND METHODS
Patient Flow
Between July 1992 and December 2003, 515 patients were diagnosed to have SCLC at the National Cancer Center Hospital East, and 474 of these patients received initial chemotherapy with or without thoracic radiotherapy. Of 474 patients, radiographic response was observed in 409 patients, with 98 demonstrating complete response and 311 demonstrating partial response. An evaluation in April 2007 revealed that among these responders, 322 had developed disease recurrence, 75 had maintained responses, and 12 patients could not be evaluated for disease recurrence. Thus, 387 patients (including the 322 with disease recurrence and the 65 nonresponders) were considered potential candidates for second-line chemotherapy. Of these, 232 received second-line chemotherapy, whereas the remaining 155 did not. There were no distinct eligibility criteria for second-line chemotherapy, and the decision to administer chemotherapy was based on the patient's general condition and willingness to undergo second-line therapy. The patient flow is shown in Figure 1. Among patients who received second-line chemo-
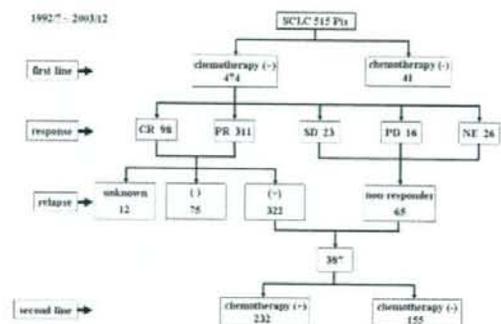
FIGURE 1. Patient flow is depicted. CR indicates complete response; NE, not evaluable; PD, progressive disease; PR, partial response; Pts, patients; SCLC, small-cell lung cancer; SD, stable disease; +, positive; −, negative.

therapy, those who deemed to have stable disease or not to be evaluable to first-line chemotherapy were treated right after completion of front-line therapy. All patients' data were obtained from our database.

Analyzed Clinical Factors
The correlations between clinical factors evaluated at the time of disease recurrence, such as the age (<70/≥70), sex (women/men), Eastern Cooperative Oncology Group performance status (PS) (0-1 or 2-4), disease extent (limited disease [LD]/extensive disease), sensitivity to first-line chemotherapy (sensitive/refractory), and response to second-line chemotherapy or survival after disease recurrence were retrospectively investigated in the 232 patients. In this study, patients who responded to initial chemotherapy and developed disease recurrence more than 3 months after the completion of chemotherapy were defined as sensitive recurrence cases, whereas patients who did not respond to initial chemotherapy or developed disease recurrence within 3 months were defined as refractory recurrence cases.

Tumor Evaluation and Statistical Analysis
Tumor response was re-evaluated by 2 physicians (Y.H.K. and K.G.) using the Response Evaluation Criteria in Solid Tumors (RECIST).[11] The survival time was measured from the date of disease recurrence. The survival curve was estimated by the Kaplan-Meier method, and compared by the log-rank test. Comparison between each clinical factor and response was performed by the chi-square test. Multivariate analysis was conducted according to the Cox proportional hazard model. $P < .05$ was considered to denote statistical significance. All statistical analyses were performed using StatView statistical

TABLE 1
Characteristics of All Patients at the Time of Disease Recurrence (N = 387)

	Second-line Chemotherapy		
Characteristics	(+) (n=232)	(−) (n=155)	P
Age at recurrence, y			<.0001
Median	65	68	
Range	30-80	28-87	
Gender			.9867
Women	38 (16%)	25 (16%)	
Men	194 (84%)	130 (84%)	
PS at recurrence			<.0001
0-1	162 (70%)	43 (28%)	
2-4	70 (30%)	112 (72%)	
Disease extent at recurrence			.0476
LD	65 (28%)	30 (19%)	
ED	167 (72%)	125 (81%)	
Response to first-line chemotherapy			<.0001
CR/PR	216 (93%)	108 (70%)	
SD/PD	16 (7%)	47 (30%)	
Sensitivity to first-line chemotherapy			.1661
Sensitive	146 (63%)	63 (41%)	
Refractory	86 (37%)	92 (59%)	

+ indicates positive; −, negative; PS, performance status; LD, limited disease; ED, extensive disease; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

software (version 5.0; Abacus Concepts, Berkley, Calif).

RESULTS
Patient Characteristics
The characteristics of the 387 patients who were believed to be potential candidates for second-line chemotherapy (of whom only 232 eventually received second-line chemotherapy, designated as the chemotherapy group) are listed in Table 1. The patients in the chemotherapy group were significantly younger ($P < .0001$), had better PS ($P < .0001$), and had a higher frequency of LD ($P = .0476$) than the nonchemotherapy group. Whereas the response to first-line chemotherapy was significantly different ($P < .0001$), the sensitivity to first-line chemotherapy was not significantly different ($P = .1661$) between the 2 groups, and approximately 33% of the patients who received second-line chemotherapy were refractory recurrence cases. As first-line chemotherapy, 156 patients (67%) had received platinum plus etoposide combination chemotherapy, and 24 (10%) had received the IP regimen. The second-line chemotherapy regimens administered to the 232 patients are listed in Table 2. At our hospital, the vast majority of the patients had received some kind of platinum-based combination chemotherapy, such as cisplatin, vincristine, doxoru-

TABLE 2
Second-line Chemotherapy Regimens Administered to 232 Patients

Regimen	No. of Patients	No. Sensitive (%)	No. Refractory (%)
CODE	80	50 (34)	30 (35)
PEI	44	17 (12)	27 (31)
IP	34	28 (19)	6 (7)
PE	19	13 (9)	6 (7)
CE	14	12 (8)	2 (2)
TOP	14	9 (6)	5 (6)
CPT-11	13	9 (6)	4 (5)
AMR	6	5 (4)	1 (1)
Others	8	3 (2)	5 (6)
Total	232	146 (100)	86 (100)

CODE indicates cisplatin, vincristine, doxorubicin, and etoposide; PEI, cisplatin, etoposide, and irinotecan; IP, cisplatin and irinotecan; PE, cisplatin and etoposide; CE, carboplatin and etoposide; TOP, topotecan; CPT-11, irinotecan; AMR, amrubicin.

TABLE 3
Univariate Analysis for Response and Survival

Characteristics	No. of Patients	Response Rate, %	P	MST, Months	P
Age at recurrence, y			.5058		.6347
<70	167	56		9.0	
≥70	65	62		8.8	
Gender			.1826		.5672
Women	38	68		10.0	
Men	194	55		8.7	
PS at recurrence			.0126		<.0001
0-1	162	63		11.0	
2-4	70	44		4.9	
Disease extent at recurrence			.5085		.0043
LD	65	62		12.6	
ED	167	56		7.3	
Sensitivity to first-line chemotherapy			.4413		.0016
Sensitive	146	60		10.6	
Refractory	86	53		6.8	

MST indicates median survival time; PS, performance status; LD, limited disease; ED, extensive disease.

bicin, and etoposide; cisplatin, etoposide, and irinotecan (PEI); IP; PE; or carboplatin plus etoposide. The distribution of these regimens was similar in the sensitive and refractory recurrence patients.

Predictive and Prognostic Factors
According to the results of the univariate analyses, response was significantly associated with the PS alone, whereas survival was significantly associated with the PS, disease extent, and sensitivity to first-line chemotherapy (Table 3). Survival curves drawn according to the PS and sensitivity to first-line chemotherapy are shown in Figure 2 and 3, respectively. Multivariate analysis identified PS ($P < .0001$) and
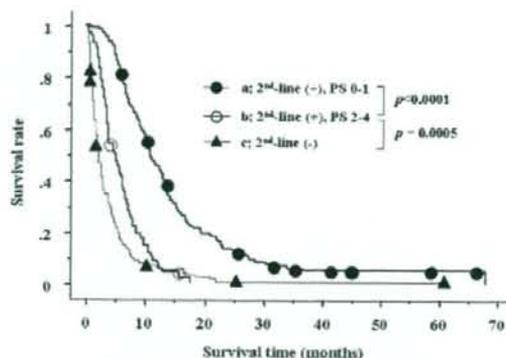
FIGURE 2. Survival curves according to the performance status (PS) at the time of disease recurrence. + indicates positive; −, negative.
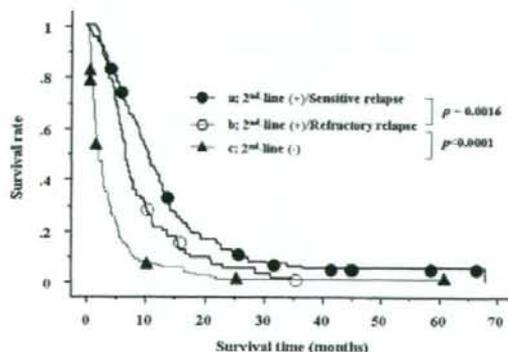

FIGURE 3. Survival curves according to sensitivity to first-line chemotherapy. + indicates positive; −, negative.

TABLE 4
Multivariate Analysis for Survival

Variables	Odds Ratio	95% CI	P
PS at recurrence, 0-1	3.171	2.307-4.357	<.0001
Disease extent at recurrence, LD	1.308	0.956-1.790	.093
Sensitivity to first-line chemotherapy, sensitive	1.544	1.166-2.043	.0024

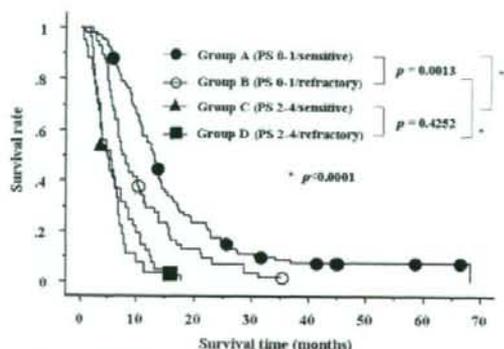95% CI indicates 95% confidence interval; PS, performance status; LD, limited disease.

FIGURE 4. Survival curves according to the 2 independent prognostic factors. PS indicates performance status.

sensitivity to first-line chemotherapy ($P = .0024$) as the independent prognostic factors for survival (Table 4). The survival of patients with a PS of 2 to 4 ($P = .005$) (Fig. 2) and refractory disease recurrences ($P < .0001$) (Fig. 3) was significantly better than that of those who did not receive second-line chemotherapy.

In addition, we performed further analysis, in which all patients who received second-line chemotherapy were divided into 4 groups according to the combination of the 2 identified independent prognostic factors for survival: Group A (PS of 0-1/sensitive recurrence), Group B (PS of 0-1/refractory recurrence), Group C (PS of 2-4/sensitive recurrence), and Group D (PS of 2-4/refractory recurrence). The survival curves for each group are shown in Figure 4. The survival of patients with a PS of 0 to 1 was significantly better than that of the patients with a PS of 2 to 4 among both cases with sensitive

(Group A vs Group C; $P < .0001$) and those with refractory recurrence (Group B vs Group D; $P = .0001$). Whereas the survival of the sensitive recurrence cases was significantly better than that of the refractory recurrence cases among the patients with a PS of 0 to 1 (Group A vs Group B; $P = .0013$), no survival difference was observed between the sensitive and refractory recurrence cases among the patients with a PS of 2 to 4 patients (Group C vs Group D; $P = .4252$).

Among the 232 patients who received second-line chemotherapy, 29 received the same regimen as first-line chemotherapy, and the rest received a regimen different from first-line chemotherapy. However, these differences did not appear to have an impact on either response ($P = .7519$) or survival ($P = .5873$).

DISCUSSION

Some studies have shown the importance of both response and the duration of the response to initial chemotherapy in predicting the survival of recurrent SCLC patients receiving second-line chemotherapy,[8-10] and currently it is widely accepted that recurrent SCLC patients should be classified into 2 groups: cases with sensitive recurrence and those with refrac-

tory recurrence.[12] In contrast, Sundstrom et al, who recently analyzed 19 clinical factors at both the time of initial diagnosis and the time of recurrence, have suggested that the PS at the time of disease recurrence, and not the sensitivity status to first-line chemotherapy, was the only significant prognostic indicator for survival after second-line chemotherapy.[13] In this study, we investigated the relation between clinical factors evaluated at the time of disease recurrence and survival after recurrence, and identified both PS and sensitivity to first-line chemotherapy as being significant prognostic factors for survival.

Some may argue that the survival time of the patients with a PS ≥3 in this study was too short, which might have strongly influenced the inferior survival of the patients with a PS of 2 to 4 as compared with that of the patients with a PS of 0 to 1. Although our study included 18 cases with a PS ≥3 among the patients administered second-line chemotherapy, the results of the analyses were found to be the same even after exclusion of these patients with a PS ≥3 (data not shown). This finding suggests that the prognosis of the patients with a PS of 2 is clearly different from that of the patients with a PS of 0 to 1 patients. The diversity of our second-line regimens may be criticized as well, because the differences in the regimens could have affected the patients' outcomes. However, to our knowledge, there are no comparative studies suggesting the superiority of any particular regimen for second-line chemotherapy. At our hospital, as shown in Table 2, mainly platinum-based combination chemotherapy is used even for second-line chemotherapy, and various agents are combined with platinum agents.

The results of the current study indicate that the prognosis of patients with impaired PS is inevitably poor. In such patients, no survival difference was found between the cases with sensitive and those with refractory recurrence. Does this mean that patients with a PS ≥2 should not receive second-line chemotherapy? A phase 3 trial comparing oral topotecan with BSC demonstrated a significant survival advantage of oral topotecan, and such survival benefit was also found to be preserved for patients with a PS of 2 who accounted for approximately 30% of the enrolled patients.[7] Conversely, with regard to the patients with a PS ≥3, there is no evidence as yet to suggest the clinical benefit of administering second-line chemotherapy. In our study, however, response rates of 64% in patients with a PS of 3 (n = 14) and 25% in patients with a PS of 4 (n = 4) were observed. These results suggest that second-line chemotherapy might be beneficial for adequately selected patients

with a PS of ≥2, although the survival benefit is limited as compared with that for the patients with a PS of 0 to 1. Further studies are required for precise selection of criteria for second-line chemotherapy.

In this study, the survival of patients who received second-line chemotherapy with a PS of 2 to 4 or refractory recurrences was still significantly better than that of those who did not receive second-line chemotherapy. However it was not surprising, because the patient selection for second-line chemotherapy was performed pragmatically, and patients who were thought to be unfit for chemotherapy were not administered second-line chemotherapy. The finding that the nonchemotherapy group had more patients with a PS of 2 to 4 and refractory recurrence, the 2 independent prognostic factors identified in this study, suggests that our patient selection was reasonable.

The prognosis of recurrent SCLC patients is generally poor, and to our knowledge no standard treatment has been established for these patients. In addition to the randomized trial comparing oral topotecan with BSC mentioned above, 2 phase 3 trials for recurrent SCLC have been reported to date.[14,15] A trial comparing intravenous topotecan with the combination of cyclophosphamide, doxorubicin, and vincristine demonstrated comparable response rates and survival; however, intravenous topotecan yielded greater symptomatic improvement for 4 of the 8 symptoms evaluated.[14] In the other trial, comparing oral topotecan with intravenous topotecan, no survival difference was observed.[15] Currently, topotecan is the only drug approved by the US Food and Drug Administration for recurrent SCLC. Recently, however, promising results of phase 2 studies have been reported for drugs other than topotecan for recurrent SCLC. In particular, amrubicin[16,17] and PEI[18,19] have been shown to yield excellent response rates and survival in not only sensitive but also refractory recurrent cases. In Japan, a phase 3 randomized trial comparing topotecan with PEI is now ongoing.

In conclusion, we identified PS and sensitivity to initial chemotherapy as being significant prognostic factors for survival in patients with recurrent SCLC treated with second-line chemotherapy. PS was also found to be predictive in terms of response. In future clinical trials of second-line chemotherapy, both PS and sensitivity to initial chemotherapy should be incorporated as stratification factors. The survival benefit of second-line chemotherapy is limited in patients with impaired PS, even among sensitive recurrence cases. Therefore, careful consideration of the potential risks and benefits is required in the treatment of these patients.

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Minireview

Emerging ethnic differences in lung cancer therapy

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Although global clinical trials for lung cancer can enable the development of new agents efficiently, whether the results of clinical trials performed in one population can be fully extrapolated to another population remains questionable. A comparison of phase III trials for the same drug combinations against lung cancer in different countries shows a great diversity in haematological toxicity. One possible reason for this diversity may be that different ethnic populations may have different physiological capacities for white blood cell production and maturation. In addition, polymorphisms in the promoter and coding regions of drug-metabolising enzymes (e.g., CYP3A4 and UGT1A1) or in transporters (e.g., ABCB1) may vary among different ethnic populations. For example, epidermal growth factor receptor (EGFR) inhibitors are more effective in Asian patients than in patients of other ethnicities, a characteristic that parallels the incidence of EGFR-activating mutations. Interstitial lung disease associated with the administration of gefitinib is also more common among Japanese patients than among patients of other ethnicities. Although research into these differences has just begun, these studies suggest that possible pharmacogenomic and tumour genetic differences associated with individual responses to anticancer agents should be carefully considered when conducting global clinical trials.
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Lung cancer is the most common malignancy worldwide. Approximately 1.2 million people are diagnosed with lung cancer annually (accounting for 12.3% of all cancers); the second most common malignancy is breast cancer (10.4%), followed by colorectal cancer (9.4%). As lung cancer almost invariably has a poor prognosis, it is the largest single cause of death from cancer in the world, with a mortality of 1.1 million annually (Stewart and Kleihues, 2003). Only 15% of lung cancer patients have a disease that is confined to the lung and are candidates for surgical resection; most patients with this disease have distant metastases or pleural effusion at the time of their initial diagnosis. These patients can be treated with systemic chemotherapy, but the efficacy of currently available anticancer agents is limited and patients with advanced diseases rarely live long.

As the development of new anticancer agents and chemotherapeutic regimens is both time and money consuming, clinical trials need to be as efficient as possible. One effort in this direction has been the adoption of global clinical trials for new agents that involve trial centres on more than one continent; this strategy enables adequate sample sizes to be obtained in a relatively short-time period and eliminates the need for redundant clinical trials with similar objectives conducted in different countries. However, whether the results of clinical trials performed in one population can be fully extrapolated to other populations remains questionable because of potential differences in trial designs, study-specific criteria, patient demographics, frequency of monitoring, and population-related

pharmacokinetics, pharmacodynamics and pharmacogenomics. Recently, these genetic and physiologic factors influencing cancer chemotherapy have been increasingly examined and reported.

CLINICAL OBSERVATIONS OF TOXICITY DURING CYTOTOXIC CHEMOTHERAPY

A comparison of phase III trials for the same drug combinations against non-small cell lung cancer conducted in different countries shows a great diversity in toxicity (Sekine et al, 2006). Among trials studying the combination of carboplatin and paclitaxel, the dose of carboplatin was fixed in all the trials, but the dose of paclitaxel was 200 mg m^{-2} in Japanese and European trials and 225 mg m^{-2} in American trials. Grades 3–4 neutropenia was noted in 88% of the patients in the Japanese trial, 15–51% of the patients in the European trials, and 6–65% of the patients in the American trials. Meanwhile, grades 3–4 febrile neutropenia was encountered in 16% of the patients in the Japanese trial, 0–9% of the patients in the European trials, and 2–4% of the patients in the American trials (Table 1). For combinations of cisplatin and docetaxel (Table 1) and cisplatin and vinorelbine (Table 2), the incidences of grades 3–4 neutropenia and febrile neutropenia were almost the same between phase III trials performed in different areas, but the doses of docetaxel and vinorelbine in the Japanese trials were lower than those in the European and American trials. Thus, neutropenia in patients receiving a combination of platinum and antimicrotubule agents may be more severe in Japanese than in Europeans and Americans. A higher frequency of grades 3–4 neutropenia in Japanese patients than in American patients was associated with combinations of cisplatin and irinotecan (65 vs

Table I Toxicity associated with a combination of platinum and taxane

| Research group | Chemotherapy dose | | No. of patients | Grades 3–4 toxicity (%) | | |
	Platinum	Taxane		NP	FNP	Reference
A combination of carboplatin and paclitaxel						
Japan	6 (AUC)	200 (mg m^{-2})	145	88	16	Ohe et al (2007)
Greece	6 (AUC)	200 (mg m^{-2})	252	15	0	Kosmidis et al (2002)
EU	6 (AUC)	200 (mg m^{-2})	309	51	4	Rosell et al (2002)
ECOG	6 (AUC)	225 (mg m^{-2})	290	63	4	Schiller et al (2002)
SWOG	6 (AUC)	225 (mg m^{-2})	206	57	2	Kelly et al (2001)
SWOG	6 (AUC)	225 (mg m^{-2})	182	—	3	Gandara et al (2004)
USA	6 (AUC)	225 (mg m^{-2})	190	65	—	Belani et al (2005)
USA	6 (AUC)	225 (mg m^{-2})	345	6	—	Herbst et al (2004)
A combination of cisplatin and docetaxel						
Japan	80 (mg m^{-2})	60 (mg m^{-2})	151	74	2	Ohe et al (2007)
ECOG	75 (mg m^{-2})	75 (mg m^{-2})	289	69	11	Schiller et al (2002)
USA	75 (mg m^{-2})	75 (mg m^{-2})	408	75	5	Fossella et al (2003)

NP, neutropenia; FNP, febrile neutropenia.

Table 2 Toxicity associated with a combination of cisplatin and vinorelbine

| Research group | Chemotherapy dose (mg m^{-2}) | | No. of patients | Grades 3–4 toxicity (%) | | |
	Cisplatin	Vinorelbine		NP	FNP	Reference
Japan	80 (day 1)	25 (days 1, 8)	145	88	18	Ohe et al (2007)
Greece	80 (day 8)	30 (days 1, 8)	204	37	11	Georgoulias et al (2005)
France	100 (day 1)	30 (weekly)	156	83	22	Pujol et al (2005)
EU	120 (day 1)	30 (weekly)	206	79	4	Le Chevalier et al (1994)
SWOG	100 (day 1)	25 (weekly)	202	76	1	Kelly et al (2001)
USA	100 (day 1)	25 (weekly)	404	79	5	Fossella et al (2003)

NP, neutropenia; FNP, febrile neutropenia.

32%, $P < 0.001$) and cisplatin and etoposide (92 vs 66%, $P < 0.001$) for the treatment of extensive small-cell lung cancer (Lara et al, 2007).

How can this ethnic difference in the severity of neutropenia be explained? One possibility is that the physiological capacity of the white blood cell production and maturation may vary among different ethnic populations. An asymptomatic reduction in neutrophils (benign neutropenia) is more commonly observed in individuals of African descent than in Caucasians, and no data on this phenomenon are available for Asians (Hsieh et al, 2007). The mechanisms are unclear, but a lower bone marrow reserve, an intrinsic marrow difference, an abnormal cytokine response, or any combination of these factors have been suggested (Hsieh et al, 2007). The lower neutrophil counts were associated with higher levels of IL-8 and granulocyte colony-stimulating factor in African volunteers. Thus, these cytokines are considered to compensate for the relatively low neutrophil counts in this population (Mayr et al, 2007). A recent report showed that ethnicity-related low neutrophil counts were associated with neutrophil elastase (ELA2) polymorphisms (C-199A), but not with serum cytokine levels (Grann et al, 2007).

ETHNIC DIFFERENCES IN DRUG METABOLISING ENZYMES

An explanation for the ethnic differences in haematological toxicity may be the varying activities of drug-metabolising enzymes and transporters that are mainly associated with polymorphisms in the promoter and coding regions of these enzymes (Fujita and Sasaki, 2007). The haematological toxicity of

docetaxel monotherapy was associated with the clearance of this agent in Asian patients, a phenomenon that can be largely explained by CYP3A4 activity (Yamamoto et al, 2000). A study conducted in the Netherlands showed that docetaxel clearance was associated with the homozygous C1236T polymorphism in the ABCB1 (p-glycoprotein) gene (ABCB1*8) but was not associated with any CYP3A4 gene polymorphisms (Bosch et al, 2006). In contrast, docetaxel pharmacokinetics were not associated with the percent decrease in neutrophil counts nor with any polymorphisms in the CYP3A4 and ABCB1 genes in American patients (Lewis et al, 2007). Another example of ethnic differences in drug-metabolising enzymes is the association between polymorphisms in genes involved in irinotecan metabolism and irinotecan-induced neutropenia. Among the patients who received irinotecan with or without another anticancer agent, grade 4 neutropenia was noted in 40–57% of the patients with UDP-glucuronosyltransfer-ase (UGT) 1A1*28 (a polymorphism in the promoter region of the UGT1A1 gene) homozygosity, whereas neutropenia was only observed in 15% or less of the patients with wild-type alleles. This association was consistent in both Asian and Caucasian patients, although the frequency of homozygosity was about 10% in Caucasians and much lower in Asians. The UGT1A1*6 allele is another polymorphism at exon 1 that is associated with defective glucuronidating function and is found almost exclusively in Asian individuals with a frequency as high as 20% (Fujita and Sasaki, 2007). UGT1A1*6 is significantly linked to polymorphisms of UGT1A7 and UGT1A9. A haplotype including UGT1A1*6 and UGT1A7*3, noted in as many as 15% of Japanese patients, and UGT1A1*6 homozygosity, noted in 7% of Korean patients, were significantly associated with decreased glucuronosyltransferase activity for SN-38 and severe neutropenia (Han et al, 2006; Fujita

et al, 2007). In 177 Japanese patients treated with irinotecan-including chemotherapy, a homozygous or double heterozygous genotype for UGT1A1*6 and UGT1A1*28 (*6/*6, *28/*28 or *6/*28) was significantly associated with severe neutropenia (Minami et al, 2007). In addition, patients with a homozygous C3435T polymorphism in the ABCB1 gene are four-fold more likely to develop grade 3 diarrhoea when treated with a combination of cisplatin and irinotecan (Lara et al, 2007).

Data on associations between polymorphisms in genes coding drug-metabolising enzymes and therapeutic efficacy remain scarce. A recent prospective study in 250 patients with metastatic colorectal cancer showed a significantly higher response rate (67 vs 40%) and a nonsignificant survival advantage (hazard ratio (HR): 0.81; 95% confidence interval (CI): 0.45–1.44) in patients homozygous for UGT1A1*28, compared with those with wild-type alleles; these outcomes were associated with a higher exposure to SN-38 (Toffoli et al, 2006). In a study of 81 NSCLC patients, those who were homozygous for UGT1A1*6 had a lower response rate (0 vs 50%, P = 0.038) and a poorer MST (7.6 vs 17.7 months, P = 0.017) as well as greater toxicities than the other patients (Han et al, 2006). The most plausible explanation for the negative effects of UGT1A1*6 on treatment outcome may be that the dose intensity or cycle number might have been reduced in patients with UGT1A1*6 because of polymorphism-associated toxicities (Fujita and Sasaki, 2007).

These pharmacogenetic analyses have been rather preliminary. Data on genotyping, pharmacokinetics, and pharmacodynamics collected from a large number of patients with different ethnic backgrounds are needed to demonstrate the cause of ethnic differences in chemotherapy-associated toxicity.

EFFICACY OF EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS

Epidermal growth factor receptor (EGFR), a cell membrane receptor with tyrosine kinase activity, is expressed in most patients with NSCLC and plays a role in cellular proliferation, inhibition of apoptosis, angiogenesis, metastatic potential, and chemoresistance. Small-molecule inhibitors of EGFR, such as gefitinib and erlotinib, have shown antitumor activity and have alleviated symptoms in NSCLC patients who were previously treated with standard chemotherapy. Two randomized phase II studies, IDEAL (Iressa Dose Evaluation in Advanced Lung Cancer)-1 (involving 210 patients and conducted in Europe, Australia, South Africa, and Japan) and IDEAL-2 (involving 216 patients and conducted in the USA), have evaluated the efficacy of gefitinib at a dose of either 250 mg daily or 500 mg daily in patients with advanced NSCLC in whom earlier platinum-based chemotherapy had failed. No difference in the response rates between the doses was noted, but an increased response rate was recorded for never smokers, women, and those with an adenocarcinoma histology, compared with patients who did not have these characteristics. In addition, the response rate was 28% in Japanese patients but only 9–12% in patients of other ethnicities (Fukuoka et al, 2003; Kris et al, 2003). A randomized phase III trial, ISEL (Iressa Survival Evaluation in Lung Cancer), of gefitinib vs a placebo in 1692 NSCLC patients who had been previously treated with one or two chemotherapeutic regimens failed to show any survival benefit of gefitinib; in the overall population, the median survival times (MSTs) in the gefitinib and placebo arms were 5.6 and 5.1 months, respectively (HR: 0.89; 95% CI: 0.78–1.03). A subgroup analysis, however, showed that the MST was longer in Asian patients receiving gefitinib than in those receiving the placebo (MST: 9.5 vs 5.5 months; HR: 0.66; 95% CI: 0.48–0.91). Similar results were seen for never smokers: patients receiving gefitinib survived longer than those receiving the placebo (MST: 8.9 vs 6.1 months; HR: 0.67, 95% CI: 0.49–0.91) (Thatcher et al, 2005).

A similar association between objective responses and ethnicity was observed in studies on erlotinib monotherapy for previously treated advanced NSCLC. In an American phase II trial of this agent in 57 advanced NSCLC patients with disease progression or relapse after platinum-based chemotherapy, the response rate was 12% and the MST was 8.4 months (Perez-Soler et al, 2004). In contrast, the combined data of two Japanese phase II trials of erlotinib in similar patient populations showed objective responses in 30 of 106 (28%) patients and an MST of 13.8 months. Among the responders, significantly higher proportions of females (50%) than males (17%) (P = 0.0009) and of never smokers (51%) than smokers (14%) were observed (P < 0.0001) (Tamura et al, 2007). A phase III trial of erlotinib or a placebo in 731 NSCLC patients previously treated with one or two chemotherapy regimens showed that the response rate in Asian patients was higher than that in patients of other ethnicities (28 vs 10%, P = 0.02) (Shepherd et al, 2005).

These results of phases II and III trials consistently suggest that EGFR tyrosine kinase inhibitors may be more effective in Asian patients than in patients of other ethnicities.

In April 2004, the activating mutations of the EGFR gene were identified in NSCLC specimens, and cancers with these mutations were reported to be highly sensitive to gefitinib. The populations with higher responses to gefitinib (females, non-smokers, and patients with an adenocarcinoma histology) also have higher incidences of EGFR mutations (Kosaka et al, 2004; Pao et al, 2004; Shigematsu et al, 2005). The incidence of EGFR mutations in surgically resected tissue samples is summarised in Table 3 (Kosaka et al, 2004; Pao et al, 2004; Marchetti et al, 2005; Qin et al, 2005; Shigematsu et al, 2005; Soung et al, 2005; Tokumo et al, 2005; Yang et al, 2005; Sasaki et al, 2006). The incidence varies from one report to another, but EGFR mutations tend to be more common among patients with an adenocarcinoma histology and among non-smokers. Among Asian patients, the average incidences of EGFR mutations were 31% overall, 47% among patients with adenocarcinoma, and 56% among non-smokers; among other ethnic populations, however, the average incidences were 7–8% overall, 13–15% among patients with adenocarcinoma, and 34–35% among non-smokers (Table 3). Thus, the percentage of responders to gefitinib or erlotinib almost paralleled the percentage of patients with EGFR mutations.

The mechanism responsible for the high frequency of EGFR mutations in Asian patients is a subject of great interest, and polymorphisms in the regulatory sequence of the EGFR gene have been vigorously investigated. The CA simple sequence repeat 1 (CA-SSR1), a highly polymorphic locus containing 14–21 CA dinucleotide repeats, is located at the 5′ end of intron 1 of the EGFR gene. Studies of CA-SSR1 repeat length and EGFR expression in breast cancer tissues have shown a constant decline in EGFR expression with increasing repeat length (Buerger et al, 2000, 2004). In addition, a shorter repeat length was associated with an elevated risk of lung cancer (Zhang et al, 2007) and poor survival in NSCLC patients (Dubey et al, 2006). The CA-SSR1 repeat length distribution varies according to ethnicity, with Asians tending to have longer repeats than Americans (Liu et al, 2003). Two single-nucleotide polymorphisms in the promoter region of the EGFR gene (−219G/T and −191C/A) were also associated with promoter activity and EGFR expression (Liu et al, 2005), and their polymorphic types (associated with low EGFR expression) were more common among Asians than among other ethnicities (Nomura et al, 2007). These observations suggest that many Asians have polymorphic types that lead to a decreased intrinsic production of EGFR protein. If a certain critical level of EGFR is required to drive the cell toward a malignant phenotype, another mechanism including activating mutations of EGFR and/or the autonomous activation of downstream signalling may be required for the development of lung cancer among Asians (Nomura et al, 2007).