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A randomized trial comparing adjuvant chemotherapy versus surgery alone for completely resected pN2 non-small cell lung cancer (JCOG9304)

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Non-small cell lung cancer;
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Summary The purpose of this study was to evaluate the efficacy of adjuvant chemotherapy with three courses of cisplatin and vindesine, in comparison to observation only, for N2 non-small cell lung cancer that had been completely resected. Patients with pathologically demonstrated mediastinal lymph node metastasis (N2), who had undergone complete resection, were randomized to observation or adjuvant chemotherapy (cisplatin 80 mg/m^2 on day 1; vindesine 3 mg/m^2 on days 1 and 8: $\times$3 courses). Cycles started within 6 weeks after complete resection and were repeated every 4 weeks. This trial was terminated before accumulation of the planned numbers for registration because of a slow accrual rate. A total of 119 patients were randomized (59 patients in the adjuvant arm and 60 with surgery alone). The median survival

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was 36 months for both groups. Postoperative cisplatin with vindesine chemotherapy was not shown to be efficacious in cases of completely resected N2 non-small cell lung cancer in this setting of timing, dose and agents studied.

1. Introduction

Even completely resected non-small cell lung cancer (NSCLC) usually relapses with distant metastases. Many adjuvant chemotherapy trials have been conducted to reduce the incidence of postoperative distant metastases. Holmes et al. reported that adjuvant cyclophosphamide, doxorubicin, and cisplatin (CAP) therapy improved disease-free survival for stage II-III adenocarcinomas [1]. Since then, many cisplatin based adjuvant chemotherapy trials have been conducted around the world. Most trials for adjuvant chemotherapy have neither reduced distant metastases nor local recurrence.

Mountain and Dresler reported that some patients with stage I (70-80%) and II (50%) disease can be cured by surgery alone [2]. For these patients, adjuvant chemotherapy would be unnecessary. Postoperative stage IIIA disease relapses in more than two-thirds of cases treated surgically. There are very few stage IIIA patients who could be cured with surgery alone, in whom adjuvant chemotherapy would be unnecessary. The Japanese Clinical Oncology Group (JCOG) conducted a randomized study of postoperative adjuvant chemotherapy focusing only on stage IIIA NSCLC [3], but showed no survival benefit of adjuvant chemotherapy compared with observation alone. There were more cases of N2 disease enrolled in the adjuvant chemotherapy group than in the surgery alone group. In Ohta's report, chemotherapy had to be administered for two or three courses, and many patients received only two cycles of chemotherapy, only 41% of the patients received three cycles of chemotherapy. In the present protocol, cycles of chemotherapy should be administered three times because the low compliance of drug delivery might have contributed to the negative result of the study of Ohta et. al. Also, the present protocol included only N2 patients so as to make the population more uniform.

2. Patients and methods

The protocol was reviewed by JCOG Clinical Trial Review Committee and approved by the Institutional Review Board of each participating hospital. Patient eligibility was dependent on the following criteria: to have undergone complete resection with systematic mediastinal dissection (as described in "General rule for clinical and pathological record of lung cancer" [4]), histologically documented non-small cell lung cancer, including squamous cell carcinoma, adenocarcinoma, large cell carcinoma or adeno-squamous cell carcinoma; age less than 75 years and World Health Organization (WHO) performance status 0-1; normal hematological data (WBC $\geq$ *4000*/mm^3, platelet count $\geq$100,000/mm^3); normal hepatic function (bilirubin $\leq$1.5 mg/dl, SGOT and SGPT within twice the normal range); and normal renal function (blood urea nitrogen $\leq$25 mg/dl, serum creatinine $\leq$1.5 mg/dl, creatinine clearance $\geq$50 ml/min). Furthermore, to be eligible, the absence of no distant metastasis prior to surgery had to be established by full staging procedures including brain computed tomography (CT) or magnetic resonance imaging (MRI), chest CT, bone scans, and abdominal CT or abdominal ultrasonography revealed. Mediastinoscopy was not mandatory before surgery. All patients had ipsilateral mediastinal lymph node metastasis. Finally, patients could not have been previously treated with chemotherapy or radiation therapy for any malignancy and could not have active secondary cancers. Written informed consent, signed by patients, was mandatory before registration.

The following were excluded.: low-grade malignant lung cancers such as carcinoid tumor, adenoid cystic carcinoma or mucoepidermoid carcinoma, N3 lymph node metastases (contralateral mediastinal, contralateral hilar, supraclavicular nodes, or scalene nodes) and cases with malignant pleural effusion or pleural dissemination, T4 disease, i.e. direct invasion to the mediastinal lymph nodes, esophagus, vertebral bodies, heart or carina. Patients with Pancoast type tumor; superior vena cava syndrome or pretracheal or paratracheal lymph node metastases from cancers in which the primary lesion was located in the left lung were also excluded.

At post-operative registration, patients were randomly assigned to either observation or adjuvant chemotherapy. Neither group was allowed to receive any other treatments for cancer other than the planned adjuvant chemotherapy until relapse.

The adjuvant chemotherapy regimen was as follows: intravenous cisplatin (CDDP) 80 mg/m^2 on day 1 and vindesine (VDS) 3 mg/m^2 on days 1 and 8, every 4 weeks for 3 cycles. Chemotherapy started within 6 weeks after surgery.

3. Statistical considerations

Randomization was carried out by a blocked arrangement that balanced the treatment assignments within each institution. All patient data, including clinical, pathological, and outcome measures were entered into a computerized database using a Stat view version 5.0 (SAS Institute Inc. Cary, NC, USA.). The chi-square test and Fischer's test were used to examine the deviation of each patient's characteristics. The Kaplan-Meier method was used to calculate survival analyses. The log-rank test and the generalized Wilcoxon test were used to determine survival differences.

We planned to enter 100 cases into each group. The benefit of adjuvant chemotherapy was assumed to be a 20% increase in the 3-year survival rate (60% in the adjuvant group and 40% in the observation group) [5,6]. Given these assumptions, 154 patients were required, assuming a type 1 error of 0.05 and a type 2 error of 0.20. The primary endpoint was overall survival. The secondary endpoints was disease-free survival. However, the accrual rate was very slow. We abandoned this study in July 1998 after acquiring permission to do so from the JCOG clinical trial review committee. The endpoint was changed to overall survival only. Follow up was done every 6 months by the JCOG data center. The final outcome was confirmed in August 2001.

4. Results

From January 1994 to July 1998, 119 cases were entered from 26 institutes. Of the 119 patients, 59 were randomized to the CDDP + VDS arm and 60 to the surgery alone arm. Only one patient was lost to follow-up.

Forty men and 19 women were included in the adjuvant chemotherapy arm, and 37 men and 23 women were included in the control arm. The median age was 62 in both groups. Pneumonectomy was performed in only six patients in each group. The two groups were well balanced in regard to sex, age, operation performed, preoperative stage, pathological T factors, pattern of combined resection and number of N2 stations (Table 1).

There were no ineligible cases. There were no toxic deaths during adjuvant chemotherapy. Thirty-five of the 59 patients assigned to the chemotherapy arm received three courses of chemotherapy, 55 patients received one or more courses of chemotherapy, and 44 patients received two or more courses. The major cause of

Table 1 Patient characteristics

	Adjuvant chemotherapy	Observation	
Gender (male/female)	40 (68%)/19	37 (62%)/23	0.48
Median age	62 (41–75)	62 (43–74)	0.93
Operation			
Pneumonectomy	6 (10%)	6 (10%)	0.97
Lobectomy	53	54	
Clinical stage			
Stage I–II	44 (75%)	41 (68%)	0.45
Stage III	15 (25%)	19 (32%)	
Pathological T			
T1–/T3	50	55	0.24
Histology			
Adenocarcinoma/squamous cell carcinoma/others	47 (80%)/9/3	40 (67%)/15/5	0.28
Combined resection			
Chest wall	6	3	0.28
Diaphragm	1	1	
Others	9	4	
None	43 (73%)	52 (87%)	
Number of N2 stations			
1	31 (52%)	28 (47%)	0.75
2	24	25	
Unknown	4	6	

Table 2 Compliance of chemotherapy and causes for discontimuation

Chemotherapy	Case no.	Cycles performed			
		0	1	2	3
Fully administered	59	4	11	10	34 (58%)
	34	0	0	0	34
Cause of discontinuation					
Adverse effect	5	0	3	2	–
Patient refusal	18	3	7	8	–
Others	2	1	1	1	–

discontinuation of the chemotherapy was patient withdrawal, which accounted for 17 cases (Table 2). There were no grade four adverse effects on hematological data during chemotherapy. The major toxicity was grade 3 neutropenia, which 50% of patients experienced. Only two patients had grade 3 bilirubinemia, and one had grade 3 creatinine elevation.

The 5-year survival was 28.2% in the chemotherapy arm and 36.1% in the control group ($P = 0.89$). The median disease-free survival was 18.3 months in the chemotherapy group and 16.1 months in the control group ($P = 0.66$). There were no statistical differences between the two groups in overall survival by either the log-rank test or the generalized Wilcoxon test (Fig. 1). Almost all deaths were from the original cancer, especially distant metastasis (46%). Lung, bone and brain were frequent sites of relapse in both groups. Lymph node relapses were more frequently seen in the observation group than the adjuvant chemotherapy group ($P = 0.049$) (Tables 3 and 4). Univariate analysis was performed to examine the following factors: treatment arm, age, gender, tumor histology, extent of surgery, existence of combined resection, and number of N2 stations (Table 5). Only an age of 61 or younger was found to be a significant favorable prognostic factor ($P = 0.042$).

5. Discussion

We set out to clarify whether adjuvant chemotherapy is effective in cases of completely resected N2 non-small cell lung cancer.

The first report of adjuvant chemotherapy for completely resected non-small cell lung cancer

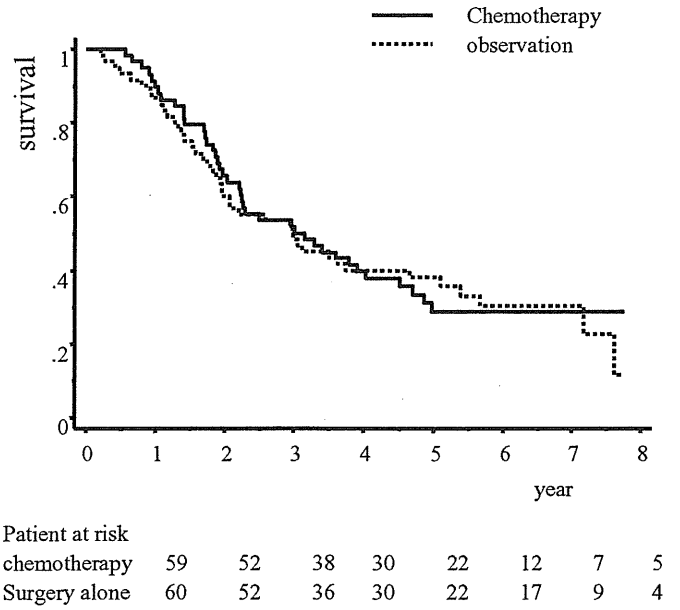

Fig. 1 Actual survival. The solid line indicates the adjuvant group and dotted line indicates the observation group ($P = 0.89$).

Table 3 Treatment-related adverse effects (WHO grade) by chemotherapy

Adverse effect	Grade 1–2 (%)	Grade 3 (%)	Grade 4 (%)
WBC	44	51	0
Hb	85	7	0
Plt	11	2	0
Bilirubin	11	4	0
SGOT	22	0	0
SGPT	24	0	0
Creatinine	25	1	0
Nausea/vomit	73	9	0
Diarrhea	16	0	0
Infection	5	2	0
Alopecia	78	—	—

Four patients who did not have chemotherapy were excluded from this analysis. $n = 55$.

Table 4 Relapse patterns for each group

Relapse site	Adjuvant chemotherapy	Observation	*P*-value
Bone	10 (2)	8 (1)	0.77
Brain	13 (1)	8	0.31
Lung	13 (2)	10 (4)	0.60
Mediastinal or cervical LN	7	18 (3)	0.049
Others	4 (1)	5	0.99

Data in parentheses represent metastasis found synchronously at another site. All data reflect absolute numbers of patients.

Table 5 Univariate analyses according to prognostic factors

Factors		*P*-value
Study arm	Adjuvant vs. obsevation	0.840
Age	≤61 vs. >61	0.042
Gender	Female vs. male	0.505
Histology	Adenocarcinoma (ad) vs. non-ad	0.220
Operation	Pneumonectomy vs. lobectomy	0.614
Combined resection	With vs. without	0.116
Number of N2 station	1 vs. 2	0.333

There is no significant difference between any factors.

using a CDDP-based regimen, reported by Holmes et al. [1], included stages II and III, and demonstrated slight effectiveness of adjuvant chemotherapy for large cell and adenocarcinoma cases. LCSG801 [7] also included T2N0 and T2N1 patients, but revealed no effectiveness of adjuvant chemotherapy for non-small cell lung cancer at all. Niiranen et al. reported another randomized trial for completely resected non-small cell lung cancers [8]. Although they demonstrated the efficacy of adjuvant chemotherapy for T1-3N0 patients, the higher number of pneumonectomies included in the observation group might have caused the difference. A meta-analysis of adjuvant chemotherapy by the Non-Small Cell Lung Cancer Collaborative Group reported that the hazards ratio in most trials slightly favored adjuvant chemotherapy but the *P*-value was not significant [9]. The 5-year survival rate for adjuvant chemotherapy patients was 5% better than for surgery alone. A BLT study (ASCO 2003, abstract#2543), which enrolled 381 patients from 56 institutes and included all stages, also could not show the effectiveness of chemotherapy. An 8% 2-year survival advantage was seen with chemotherapy in another meta-analysis for node positive patients [10]. Therefore, the selection of particular stages for perioperative chemotherapy may have been the key to the success seen in that adjuvant chemotherapy trial.

Dautzenberg reported a randomized trial that compared adjuvant radiation versus adjuvant radiation plus chemotherapy [11]. They found no significant difference in overall survival. However, in the subset analyses, patients with N2 disease treated with chemoradiation had a significantly better survival than radiation alone. Keller also reported no difference between survival rates for adjuvant chemo-radiotherapy and adjuvant radiotherapy for stage II and IIIa cancers [12]. Although there have been many clinical trials for non small cell lung cancer, there have been almost no reports on clinical trials of adjuvant chemotherapy for n2 disease. Only Pisters et al. [13] made a report on comparing adjuvant chemo-radiotherapy and adjuvant radiotherapy limited to 71 cases of T1-2 N2 disease including incompletely resected patients. They also did not demonstrate any therapeutic effectiveness. There are several large-scale randomized control studies of adjuvant chemotherapy for patients with completely resected lung cancers. An ALPI study (ASCO 2002, abstract#1157) reported ineffective results, while an IALT study (ASCO 2003, abstract#6) showed slight efficacy of adjuvant chemotherapy. Those two trails included radiation therapy frequently for patients with nodal metastasis. Those reports, mentioned above, aimed to

determine the efficacy of adding chemotherapy to radiation therapy after surgery for patients with nodal metastasis. PORT meta analysis reported that post operative radiation therapy was not useful even in nodal metastasis patients [14], so we aimed to determine the efficacy of adding chemotherapy after surgery for patients with mediastinal nodal metastasis without radiation therapy.

Ohta et al. reported an adjuvant trial for stage IIIa disease conducted by JCOG [3], which also revealed no effectiveness of adjuvant chemotherapy. Although the patients were randomly assigned to each group, the surgery alone group included a higher number of N2 disease patients than the adjuvant chemotherapy group, which may have been related to the negative result. We enrolled only completely resected N2 disease to reduce the heterogeneity of diseases.

Compliance is important in adjuvant chemotherapy. LCSG801 [7] was criticized for low compliance, which was seen as one possible reason for negative data. In our series, 58% of patients received the targeted dose and 75% received two or more courses without serious adverse effects. This appeared sufficient for adjuvant chemotherapy. Although the number of patients accrued was small, the two survival curves were almost identical. Thus, in pathological N2 disease, adjuvant chemotherapy using CDDP and VDS does not improve survival.

The initial target of neoadjuvant chemotherapy was only locally advanced cancer. A few small-sample trials have shown some efficacy of perioperative chemotherapy [15,16]. Recently, a Bimodality Lung Oncology Trial (BLOT) study focused on earlier stages as a target for chemotherapy [13]. The French trial for neoadjuvant chemotherapy also included stages I-IIIa [17]. These two groups hold great expectations for perioperative chemotherapy in earlier stages. Considering these studies, adjuvant chemotherapy is also warranted with new agents for earlier stages of cancer.

6. Conclusion

Patients with N2, NCSLC who had undergone complete resection, were randomized to surgery only or adjuvant chemotherapy (cisplatin 80 mg/m^2 on day 1; vindesine 3 mg/m^2 on days 1 and 8; $\times$3 courses). This trial was terminated before accumulation of the planned numbers for registration because of a slow accrual rate. A total of 119 patients were randomized (59 patients in the adjuvant arm and 60 with surgery alone). The median survival was 36 months for both groups. There was no significant difference in survival between the adjuvant chemotherapy group and the observation group. The efficacy of adjuvant chemotherapy for completely resected NSCLC with N2 disease might be so small that the number of patients in this study was insufficient to detect the efficacy of this classic regimen.

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Gefitinib in the adjuvant setting: safety results from a phase III study in patients with completely resected non-small cell lung cancer

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Standard therapy for stage I–IIIA non-small cell lung cancer (NSCLC) is surgery, although adjuvant therapies are required to prevent disease recurrence and improve patient survival. This is the first study that planned to administer adjuvant gefitinib (Iressa) 250 mg/day or placebo to randomized patients with completely resected NSCLC (stage IB–IIIA) 4–6 weeks following surgery, for 2 years, until recurrence/withdrawal. However, recruitment was stopped after the randomization of 38 patients, because interstitial lung disease (ILD)-type events were being increasingly reported in Japan in the advanced disease setting. Finally, the trial was halted. Safety data for 38 recruited patients (18 gefitinib and 20 placebo) showed no unexpected adverse drug reactions (ADRs), with the most common being grade 1/2 gastrointestinal and skin disorders in 12 and 16 patients receiving gefitinib and in five and six patients receiving placebo, respectively. Grade 3/4 ADRs occurred in four patients receiving gefitinib and one patient receiving placebo. ILD-type events were reported in one patient receiving gefitinib (concomitantly with other ILD-inducing drugs) who died and two patients receiving placebo. Eight patients receiving gefitinib withdrew due to ADRs compared with three patients receiving placebo. Adverse events associated with surgical complications were reported for six patients receiving gefitinib and four patients receiving placebo. In the adjuvant setting there were no unexpected adverse events observed. Gefitinib had no impact on surgery-related complications when given within 4–6 weeks post-operatively. *Anti-Cancer Drugs* **16:1123–1128 © 2005 Lippincott Williams & Wilkins.**

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Keywords: gefitinib, non-small cell lung cancer, phase III, safety

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Introduction

Non-small cell lung cancer (NSCLC) is generally not diagnosed until the disease is symptomatic, by which time more than two-thirds of patients are in the advanced stages of disease and have a poor prognosis [1]. Approximately 25% of patients with NSCLC are diagnosed when their disease is in the early stages; however, as many of these patients frequently have undetectable metastases, disease often recurs in distant sites [2]. Adjuvant therapies are therefore required to help prevent disease recurrence and as they will need to be given to patients post-operatively for a prolonged period, they should be well tolerated.

Although some clinical trials in NSCLC have shown a significant survival benefit with adjuvant uracil plus tegafur (UFT) and cisplatin-based chemotherapy [3–7], others have not observed a significant improvement in survival [5,8,9]. At the time of commencing this study, there were no standard adjuvant treatment regimens for NSCLC.

Gefitinib (Iressa), an orally active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), was approved in Japan for the treatment of inoperable or recurrent NSCLC in 2002. Two large phase II trials, IDEAL (Iressa Dose Evaluation in Advanced Lung cancer) 1 and 2, observed objective responses and stable disease in more than 40% of pre-treated patients with NSCLC receiving 250 mg/day gefitinib, with the majority of adverse events (AEs) being mild to moderate gastrointestinal and skin disorders [10,11]. Gefitinib was not associated with the well-recognized AEs observed with cytotoxic chemotherapy (e.g. bone marrow depression, neurotoxicity, nephrotoxicity). The tolerability profile of gefitinib has been confirmed by data from the

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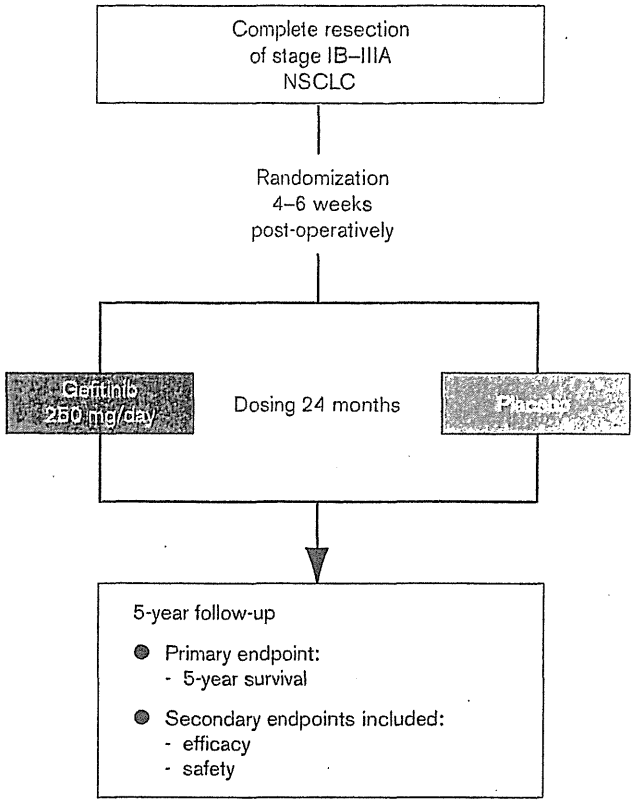
Expanded Access Programme, through which more than 39 000 patients have received gefitinib 250 mg/day on a compassionate-use basis. Furthermore, a retrospective analysis of 9515 US patients who had received gefitinib for 1 year or more via the Expanded Access Programme showed a 1-year survival rate of 33% [12], which compares with the IDEAL studies [10,11]. Recently, Onn *et al.* observed efficacy (16% with objective responses and 45% with stable disease) and a low incidence of grade 3/4 AEs in Japanese patients with NSCLC, most of whom had been treated with second-line gefitinib or above (99% of patients) [13].

To date, there is no experience of using gefitinib in the post-operative adjuvant setting. This phase III trial was initially undertaken to compare survival rates in patients with completely resected stage IB–IIIA NSCLC who had been treated with adjuvant gefitinib 250 mg/day or placebo. However, in October 2002, recruitment was halted following high-profile media activity around reports of gefitinib-related interstitial lung disease (ILD)-type events in patients with advanced or metastatic NSCLC in Japan. In March 2003, the trial was halted because of an increased withdrawal rate. As enrollment could not be resumed until the prospective investigation into gefitinib-related ILD-type events in Japan was completed, the trial was closed. Consequently survival data are not available, although data from patients recruited to the study have been subsequently analyzed for safety.

Fig. 1



Trial design schema.

Methods

Patients

Patients were eligible for inclusion in the trial if they had histologically confirmed NSCLC (post-operative stage IB–IIIA) that had been completely resected 4–6 weeks before the start of treatment. Patients were required to be 20–75 years of age, with a WHO performance status (PS) 0–1, no previous history of chemotherapy, radiotherapy or immunotherapy for NSCLC and no co-malignancies within the past 5 years. All patients gave written, informed consent to participate in the trial, which was conducted in accordance with the Declaration of Helsinki [14] and Good Clinical Practice guidelines.

Study design

This randomized (1:1), double-blind, placebo-controlled, phase III multicenter survival study planned to recruit 670 patients (335 per group) and randomize them to receive either gefitinib (250 mg) or placebo (Fig. 1). Treatment was to be continued for 2 years, or until recurrence/secondary carcinoma or withdrawal criteria were met. An Independent Data Monitoring Committee (IDMC) was set up to assess the efficacy and safety of gefitinib post-operatively, and would advise whether the study should be continued, changed or discontinued.

Assessments

Efficacy

Disease recurrence or secondary carcinogenesis were assessed using X-rays every 3 months during treatment and every 6 months during the follow-up period. Computed tomography (CT) scans were carried out 8 weeks after the first dose (where necessary, the pre-operative thoracoabdominal CT scan could be used), at week 48 during treatment, at week 104 after withdrawal/completion and every 52 weeks thereafter, unless disease recurrence was observed.

Safety

AEs were to be recorded and coded using MedDRA (Medical Dictionary for Regulatory Activities) version 6.0, graded using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 and assigned causality by the investigators. AEs associated with post-operative complications were defined as events occurring within 90 days after surgery and were recorded without regard to causality. Treatment could be interrupted for up to 14 days, although the IDMC later recommended that drug interruption could be allowed for more than 14 days in cases where ILD-type events were suspected, but could not be confirmed, in order to ensure the safety of

patients who remained in the trial after recruitment was halted. Hematology, biochemistry and urinalysis were also measured at baseline and during the study.

Role of the funding source

This trial was coordinated and supervised by the principal investigators, the IDMC and AstraZeneca personnel, with funding and organizational support from the trial sponsor AstraZeneca.

Results

Patients

Between August and October 2002, 38 patients were randomized into the trial – 18 received gefitinib and 20 received placebo. Patient demography was well balanced between the treatment arms, with the majority of patients having adenocarcinoma histology and WHO PS 1 (Table 1). When the trial was stopped, four patients in the gefitinib arm and 11 patients in the placebo arm were still receiving treatment (Fig. 2). Of the 23 patients who withdrew, 13 did so because of AEs (10 in the gefitinib arm and three in the placebo arm), five were unwilling to continue with treatment (three in the gefitinib arm and two in the placebo arm), two had disease recurrence (both in the placebo arm) and three withdrew for other reasons (one patient in the gefitinib arm had incomplete recovery from surgery that was not drug related, and two patients in the placebo arm had pre-existing interstitial pneumonia and were withdrawn at the request of the sponsor).

Table 1 Patient demography

	Gefitinib 250 mg/day ($n=18$)	Placebo ($n=20$)
Sex [*n* (%)]		
male	14 (77.8)	15 (75.0)
female	4 (22.2)	5 (25.0)
Median age [years (range)]	64.0 (49–73)	62.5 (52–73)
WHO PS [*n* (%)]		
0	5 (27.8)	9 (45.0)
1	13 (72.2)	11 (55.0)
Histology [*n* (%)]		
squamous cell carcinoma	4 (22.2)	6 (30.0)
adenocarcinoma	14 (77.8)	14 (70.0)
Stage [*n* (%)]		
IB	7 (38.9)	8 (40.0)
IIA	2 (11.1)	1 (5.0)
IIB	3 (16.7)	5 (25.0)
IIIA	6 (33.3)	6 (30.0)

Efficacy

From the limited efficacy data, disease recurrence was not seen in patients receiving gefitinib at data cutoff. Three patients who received placebo (one with stage IB and two with stage IIB) experienced disease recurrence – two patients recurred during the trial and one patient recurred after the trial had stopped.

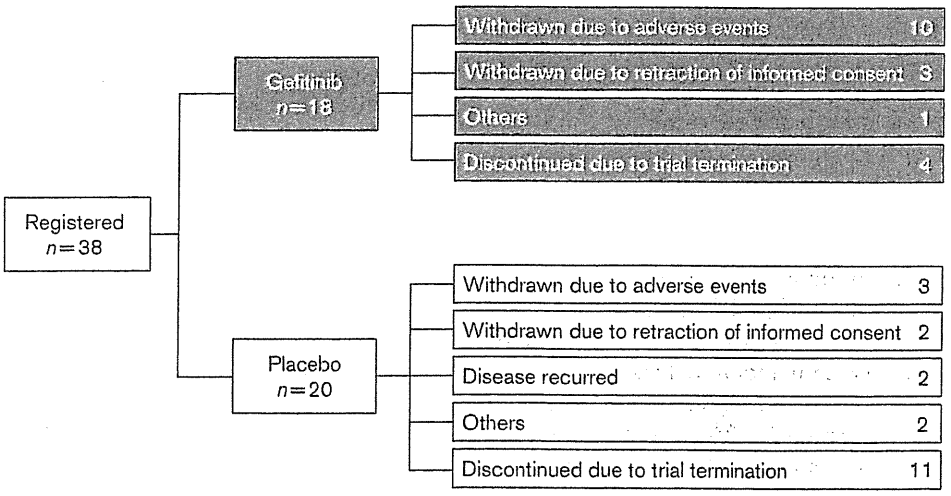
ADRs

No unexpected ADRs were observed and, in general, the frequency of all ADRs was higher for gefitinib versus placebo (Table 2). The most common ADRs were mild to moderate grade 1/2 gastrointestinal and skin disorders. Grade 3/4 ADRs were seen in four patients in the gefitinib arm and one patient in the placebo arm (Table 3), all of whom had treatment withdrawn (the patient with grade 3 eczema had treatment withdrawn due to grade 2 impetigo).

Respiratory ADRs

The majority of respiratory ADRs were grade 1/2 and occurred within 1 month of treatment. In the gefitinib arm, two patients experienced cough (associated with post-operative complications), one patient had dyspnea,

Fig. 2



Trial outcome.

Table 2 Common ADRs occurring in two or more patients

AE (MedDRA term)[a]	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Abnormal hepatic function	4	0
Acne	2	0
Anorexia	5	1
Cough	2[b]	1
Diarrhea	9	2
Dry skin	3	0
Eczema	8	2
Elevated ALT/AST	2	0
Fatigue	2	0
Gastritis	3[b]	0
Loose stools	4	0
Nausea	3	0
Rash	5	3
Sputum	0	2
Stomatitis	2	0

[a]A patient could have more than one AE.
[b]All were associated with post-operative complications.

Table 3 Grade 3/4 ADRs

AE (MedDRA term)	Grade	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Abnormal hepatic function	3	1	0
Eczema	3	1	0
Elevated ALT	3	1	0
Neutropenia	3	0	1
Pneumonitis	4	1	0

Table 4 Exposure of patients to gefitinib

	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Median duration of treatment [days (range)]	86.5 (4–195)	144.0 (20–197)
Dosing period (n)		
<60 days	6	2
60–120 days	9	4
≥ 120 days	3	14
No. dose interruptions (n)		
1	5	6
2	2	2
≥ 3	2	2

Table 5 ADRs leading to patient withdrawals

Adverse event (MedDRA term)	Grade	Gefitinib 250 mg/day (n=18)	Placebo (n=20)
Eczema	2	1	0
Elevated ALT/AST	2	1	0
	3	1	0
Hepatic function abnormalities	2	1	0
	3	1	0
ILD	1	0	1
Impetigo	2	1	0
Neutropenia	3	0	1
Paronychia	2	1	0
Pneumonitis	4	1	0
Pulmonary fibrosis	1	0	1

and one patient experienced grade 4 ILD-type events (pneumonitis) 107 days after starting gefitinib and was withdrawn from the study. The patient with pneumonitis had taken concomitant shosaikoto, a Chinese herbal medicine, and loxoprofen, both of which have previously been shown to induce pneumonitis [15,16]. Twenty-one days later bacterial pneumonia related to methylprednisolone therapy was diagnosed, and the patient subsequently died 37 days later due to both pneumonitis and bacterial pneumonia. In the placebo arm, one patient who experienced cough and grade 1 pulmonary fibrosis had had interstitial changes on their chest X-ray at enrollment, and in a second patient, pre-existing non-specific interstitial pneumonia was exacerbated resulting in grade 1 ILD. In both patients, these conditions persisted following withdrawal of study drug.

Interruptions and withdrawals due to ADRs

ADRs requiring interruptions in therapy were similar between patients receiving gefitinib or placebo (Table 4) and were usually for less than 14 days, although four patients in the gefitinib arm required treatment to be interrupted for 14 days (including one patient whose treatment was interrupted for 20 days). The majority of ADRs leading to withdrawal were usually mild-to-moderate grade 1/2 in severity (Table 5). Grade 3 ADRs leading to withdrawal occurred in two patients receiving gefitinib (hepatic function abnormalities, elevated ALT) and in one patient receiving placebo (neutropenia), and grade 4 pneumonitis led to the withdrawal of one patient who was receiving gefitinib. Following withdrawal of gefitinib treatment, grade 3 abnormal hepatic function and elevated ALT resolved, and grade 3 neutropenia persisted.

AEs associated with post-operative complications

As there are no safety data regarding the use of gefitinib in the post-operative setting, AEs associated with the healing process were examined to provide preliminary safety data on the start of the dosing timing in the adjuvant setting for gefitinib. AEs related to post-operative complications were observed in six patients in the gefitinib arm and four patients in the placebo arm. In the gefitinib arm, the most frequent AEs were grade 1/2 cough (four patients) and gastritis (three patients), and in the placebo arm grade 1/2 pain (three patients). Grade 1 cough, grade 1 supraventricular arrhythmia and grade 2 dyspnea were also experienced by three out of four patients receiving placebo.

Discussion

This trial was designed to compare survival rates in patients with completely resected stage IB–IIIA NSCLC who had received adjuvant therapy with gefitinib 250 mg/day or placebo. However, incidences of ADRs of ILD-

type events in the advanced disease setting have been increasingly reported since gefitinib was launched in Japan, and new recruitment was put on hold on 23 October 2002 at the request of the Ministry of Health, Labor and Welfare. In order to evaluate the ILD and ensure the safety of the trial patients, two separate Co-ordination Committee and JDMC meetings (December 2002 and January 2003) were conducted to discuss the feasibility of continuing the study and management of the trial patients. Based on the updated information on ADRs of interstitial pneumonia, the committees concluded that the study could be continued because the possibility of risk did not exceed that of benefit to enrolled patients. The JDMC also suggested that top priority should be given to assure the safety of the patients receiving gefitinib, and that discontinuation should be considered if flu-like symptoms including difficulty in breathing, fever and coughing occurred.

A 'Supplemental Explanation Sheet and Informed Consent Form' was provided four times to enrolled patients, offered updated information and methods to assure and manage any safety issues, and confirmed the patients' willingness to continue participating in the study. In December 2002, AstraZeneca KK gave the principal investigators the option to suspend gefitinib treatment at once. With the extensive monitoring of the trial patients in terms of safety, there were still an increasing number of withdrawals. In addition, enrollment could not be resumed until the prospective investigation on gefitinib-related ILD was completed. Based on these facts, the sponsor finally decided to terminate the trial in March 2003.

The types of AEs reported in this trial were similar to that already reported in the large phase II IDEAL 1 and 2 trials for patients with locally advanced or metastatic NSCLC [10,11]. Three patients experienced ILD-type events – two in the placebo arm and one patient in the gefitinib arm (this patient was also taking two other medications known to induce ILD) [15,17]. It has generally been observed that a higher frequency of ILD-type events are reported in Japanese patients taking gefitinib compared with those in other south-east Asian countries and the rest of the world (1.6, 0.3, and 0.3%, respectively) [18]. The occurrence of ILD in Japanese patients and the reasons for such an ethnic stratification in ILD incidence following gefitinib treatment require further clarification.

The most common reason for withdrawal in both treatment arms was due to toxicity, with the majority of drug-related AEs being grade 1/2 in severity. In the advanced or metastatic disease setting, few patients who experience grade 1/2 drug-related AEs withdraw from treatment with gefitinib, and in IDEAL 1, which recruited Japanese patients, two out of 103 patients who received gefitinib 250 mg/day withdrew from therapy due to ADRs [18]. Several factors may explain the high number of withdrawals (including withdrawal of treatment for less severe ADRs) reported in this trial data compared with previously reported studies. These reasons include the fact that patients with early-stage NSCLC may be less tolerant of AEs compared with patients with advanced NSCLC who have received prior chemotherapy. In contrast to the other studies, the impact of heavy media coverage surrounding gefitinib-related ILD cannot be ignored.

It has been suggested that the dosage and schedule of gefitinib used in this study may not best suit patients with completely resected NSCLC in terms of tolerability and a number of adjustments may need to be taken into consideration when planning an adjuvant study of gefitinib in the future. It is unlikely that the time frame of 4–6 weeks is too short before starting adjuvant treatment, as other adjuvant trials conducted in Japanese patients have used similar time frames [3,4]. It may be possible to lengthen the duration by which gefitinib could be interrupted for toxicity, since 14 days may be too short for patients recovering from AEs such as hepatic enzyme elevation, or to reduce the dose following toxicity to perhaps 250 mg every other day, although this would require further study into the efficacy of such an approach.

With no experience of using gefitinib in post-operative patients there was a concern that EGFR-TKIs might impact on surgery-related complications (especially on the healing process) due to their mode of action. In order to assess this, the trial was designed to allow a safety review of the first 60 patients. Due to the early termination of the study, we have only 38 patients' (18 on gefitinib) data for review; however, there does not seem to be any impact on surgery-related complications when gefitinib was administered within 4–6 weeks after surgery, as evidenced by a similar number of these AEs that occurred in both groups. This indicates that it may be feasible to administer gefitinib in the adjuvant setting within this time frame.

In conclusion, this is the first study to investigate the use of EGFR-TKIs as adjuvant therapy. Despite the absence of survival data, there were no unexpected AEs seen in the adjuvant setting compared with those already reported for patients with locally advanced or metastatic NSCLC. However, it was observed that there were more AEs leading to withdrawal in the gefitinib arm, even though the majority of AEs were grade 1/2 in severity, suggesting that a daily dose of gefitinib 250 mg may not best suit patients with completely resected NSCLC in terms of tolerability.

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General Thoracic Surgery

Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I-IIIa small cell lung cancer: The Japan Clinical Oncology Lung Cancer Study Group Trial (JCOG9101)

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Objective: Indications for surgical intervention for very limited small cell lung cancer have not yet been determined. The objective of this study is to determine whether resection followed by cisplatin and etoposide is feasible.

Methods: From September 1991 through December 1996, 62 patients with completely resected small cell lung cancer who were less than 76 years of age from 17 centers were entered in the trial. Of 62 patients, 61 were eligible, with a median follow-up of 65 months. Chemotherapy consisted of 4 cycles of cisplatin (100 mg/m^2, day 1) and etoposide (100 mg/m^2, days 1-3). There were 49 (80%) male patients, 44 with clinical stage I disease, 10 with stage II disease, and 6 with stage IIIa disease.

Results: Forty-two (69%) patients received 4 cycles of cisplatin and etoposide. No treatment-associated mortality was noted. Median survival time was not reached in patients with pathologic stage I disease, was 449 days in patients with stage II disease, and was 712 days in patients with stage IIIa disease. Three-year survival was 61% overall, 68% in patients with clinical stage I disease, 56% in patients with stage II disease, and 13% in patients with stage IIIa disease ($P = .02$). Recurrence was noted in 26 (43%) patients overall. Local failure was noted in 6 (10%) patients. Locoregional recurrence tends to be found more frequently in patients with stage IIIA disease. Distant failure was found in 21 (34%) patients overall. Brain metastasis was found in 15% of the patients.

Conclusion: Major lung resection followed by postoperative cisplatin and etoposide is feasible, with a favorable survival profile. Because nodal metastasis appears to be a major prognostic factor, preoperative evaluation of nodal status remains a major concern.

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The prognosis of lung cancer remains poor, and this disease is the leading cause of cancer mortality worldwide. Small cell lung cancer (SCLC) comprises approximately 20% of lung cancer cases. Without treatment, SCLC has the most aggressive clinical course of any other type of lung cancer, resulting in a very short median survival time of approximately 2 to 4 months. Although surgical resection is generally indicated for early stage non–small cell lung cancer, this is not always the case with SCLC. This can be explained by the fact that

dissemination to regional lymph nodes or distant organs would be found in most patients with SCLC at the time of initial presentation.[1] Therefore, localized forms of treatment, such as surgical resection or radiation therapy, rarely produce long-term survival, and systemic treatment with current chemotherapy regimens is usually incorporated into the treatment program.

Indications for surgical resection for SCLC have not yet been determined, although several authors have reported that a small minority of patients with limited-stage disease and adequate lung function might benefit from surgical resection.[1-9] According to these reports, the prognosis of resected SCLC was not so poor, especially when no pathologic nodal involvement was observed. The 5-year survival ranged from 26% to 61% in these trials if the tumor was stage I. Because SCLC tends to be disseminated and the results of surgical intervention alone for this disease have been reported to be poor,[1,10] postoperative chemotherapy has been used in most studies. However, the chemotherapy was not standardized, and various chemotherapy protocols were often used. Furthermore, most previous studies were retrospective and thus suffered from the inherent weakness of any retrospective assessment of a given treatment.

Because the combination of cisplatin and etoposide has been considered to be standard in the treatment of SCLC,[11] this combination was selected as a postoperative adjuvant regimen. We conducted a prospective study of surgical resection plus adjuvant chemotherapy for stage I through IIIA SCLC to investigate the efficacy of this treatment strategy.

Patients and Methods

Eligibility

Patients who were given postoperative diagnoses of SCLC histologically or cytologically were eligible for enrollment in the study. The patients had to have completely resected pathologic stage I, II, or IIIA disease according to the TNM classification of the International Union Against Cancer.[12] Histologic typing was determined according to the World Health Organization classification.[13] Inclusion criteria included an Eastern Cooperative Oncology Group performance score of 0 or 1, age between 20 and 75 years, no prior treatment for lung cancer, no other concurrent or previous malignancies, a leukocyte count of greater than 3500/μL, a platelet count of greater than 100,000/μL, a hemoglobin level of greater than 9.5 g/dL, a serum creatinine level of less than 1.5 mg/dL, and aspartate aminotransferase–alanine aminotransferase values of less than twice the institutional upper limit of normal. Exclusion criteria included a history of myocardial infarction within the past 3 months, hepatic cirrhosis, and/or severe cardiopulmonary dysfunction that required oxygen therapy. The following preoperative investigations were performed before entry into the study: computed tomographic (CT) scanning of the chest, upper abdomen, and brain; bronchoscopy; chest plain film; radionuclide bone scanning; complete blood cell count and serum chemistry; and physical examination. Preoperative mediastinoscopy was performed in some cases. All patients provided written informed consent before entering the study.

Treatment Schedule

Major lung resection, such as pulmonary lobectomy or pneumonectomy, was required as a surgical procedure for SCLC. Complete hilar and mediastinal lymph node dissections were recommended on the basis of the lymph node map defined by Naruke and colleagues.[14] After confirming complete resection and histologic typing of SCLC histologically, eligible patients were registered in the study.

Chemotherapy consisted of cisplatin (100 mg/m^2 on day 1) and etoposide (100 mg/m^2 on days 1-3; PE regimen). This regimen was repeated every 4 weeks and was administered in 4 courses. The dose was modified according to the blood cell count and renal function on the day of chemotherapy. Chemotherapy was administered unless the leukocyte count was less than 3000/μL or the platelet count was less than 75,000/μL. Chemotherapy was withheld until the counts recovered. If grade 4 hematologic toxicity, according to World Health Organization (WHO) criteria,[15] was seen, the dose of etoposide was reduced to 75%. Chemotherapy was permanently discontinued at any time when the serum creatinine level was 2.0 mg/dL or greater or the blood urea nitrogen level was 30 mg/dL or greater. To assess toxicity, we subjected all patients to complete blood cell counts and blood chemistry evaluations, such as for aspartate aminotransferase–alanine aminotransferase, blood urea nitrogen, and serum creatinine, as well as chest plain film and urinalyses at least once per week during treatment. Toxicity criteria were evaluated on the basis of the WHO criteria.[15]

Patients were followed up at the outpatient department every 3 months postoperatively and underwent CT scans of the chest, upper abdomen, and brain, as well as radionuclide bone scanning every 6 months, even when they were asymptomatic. No postoperative radiotherapy was applied until relapse was apparent.

Sites of relapse were determined by clinical, radiologic, or histologic criteria at initial recurrence. Local failure was defined as recurrence at the primary lung site or hilar-mediastinal lymph nodes. Distant failure was defined as recurrence in the contralateral lung, bone, brain, liver, or other extrathoracic regions.

Statistical Analysis

The trial was designed as a prospective phase II trial. The primary goal of the study was to estimate the survival. A sample size of 30 was considered to provide a power of 90% for detecting a significant improvement in the 3-year survival (from 20% to 50%) in a 1-sided test with an α value of .025 and a β value of .10. The median follow-up period for 35 surviving patients was 65 months. The length of survival was defined as the interval in months between the day of surgical resection of lung cancer and the date of death from any cause or the last follow-up. The survival curves were constructed by using the Kaplan-Meier method,[16] and curves were compared with the log-rank test.

Results

Patient Characteristics

Between September 1991 and December 1996, 62 patients were entered in this phase II trial at the 16 institutions that

TABLE 1. Patient characteristics

Total	61
Sex	
Male	49
Female	12
Age (y)	
Range	22-74
Median	64
Histologic subtype defined by WHO*	
Oat cell type	9
Intermediate type	45
Combined type	7
Clinical stage	
I	44
II	9
IIIA	8
Side of primary tumor	
Right	32
Left	29
Operative procedure	
Lobectomy	57
Pneumonectomy	4
Extent of lymph node dissection†	
Complete hilar and mediastinum	59
Only hilar	2
Pathologic stage	
I	35
II	8
IIIA	18
Performance status	
0	32
1	29

*Histologic subtyping was determined on the basis of the World Health Organization (WHO) classification. †The extent of lymph node dissection was defined by Naruke and associates.[14]

participated in the study. One patient was excluded because his final histologic category was changed from SCLC to large cell carcinoma. Thus, 61 patients were eligible for assessment of survival data, and their characteristics are shown in Table 1. The median age was 64 years (range, 22-74 years). According to histologic typing defined by the WHO, oat cell, intermediate, and combined types were found in 9, 45, and 7 patients, respectively. Forty-four patients had clinical stage I disease, 9 had stage II disease, and 8 had stage IIIA disease. Pathologically, stage I, II, and IIIA disease was found in 35, 8, and 18 patients, respectively.

Treatment Administration

As a surgical procedure, pulmonary lobectomy was performed in 57 (93%) patients, and pneumonectomy was performed in the other 4 patients. Among 4 pneumonectomies, 3 were on the left side, and 1 was on the right side. Complete hilar and mediastinal lymph node dissection was performed in 59 (97%) patients.

TABLE 2. Treatment delivery

Total no. of patients	61
No. of chemotherapy courses	
0	1 (2%)
1	5 (8%)
2	8 (13%)
3	5 (8%)
4	42 (69%)

A total of 204 courses were administered (Table 2). Forty-two (69%) patients underwent a full course of chemotherapy. The other 19 patients did not complete postoperative chemotherapy because of progressive disease in 3 patients, adverse effects in 7 patients, refusal of chemotherapy in 8 patients, and death from pneumonia in 1 patient.

Treatment-Related Toxicity

No treatment-associated deaths were found. Postoperative bronchopulmonary fistula was found in 1 (2%) patient who underwent pulmonary lobectomy after completion of the first cycle of chemotherapy. Chemotherapy-related toxicity is shown in Table 3. Grade 4 toxicity was found in 9 (15%) patients: leukopenia in 4 patients, thrombocytopenia in 2 patients, nausea in 2 patients, and cardiac failure in 1 patient. One patient died of pneumonia 2 months after the first course of chemotherapy, but this was not considered to be chemotherapy related.

Survival

Survival data are shown in Table 4. Among the 61 eligible patients, 35 were still alive after a median follow-up of 65

TABLE 3. Chemotherapy-related toxicity in 60 eligible patients treated for resected stage I to IIIA SCLC

	WHO grade				
Toxicity	1	2	3	4	4 (%)
Anemia	9	29	16	0	0
Leukocytopenia	7	17	26	4	6.5
Thrombocytopenia	11	8	14	2	3.2
Infection	2	1	0	0	0
Nausea	24	13	13	2	3.3
Diarrhea	8	2	2	0	0
Azotemia	35	0	0	0	0
Renal failure	18	0	0	0	0
Stomatitis	14	1	1	0	0
Dyspnea	5	0	0	0	0
Fever	10	7	0	0	0
Skin	4	2	0	0	0
Alopecia	13	23	11	0	0
Cardiac dysfunction	5	2	1	1	1.7
CNS	1	1	1	0	0
Peripheral neuropathy	5	1	0	0	0

WHO, World Health Organization; *CNS,* central nervous system.

TABLE 4. Survival in patients with resected SCLC who underwent postoperative chemotherapy

	Median survival time (d)	Survival 3 y	Survival 5 y
Clinical stage			
IA	Not reached	70%	66%
IB	Not reached	65%	65%
II	Not reached	56%	56%
IIIA	530	13%	13%
Pathologic stage			
IA	Not reached	78%	73%
IB	Not reached	67%	67%
II	449	38%	38%
IIIA	712	39%	39%

months. The overall estimated 3- and 5-year survivals were 61% and 57%, respectively (Figure 1). The 5-year survival was 66%, 56%, and 13% in patients with clinical stage I, II, and IIIA disease, respectively (Figure 2). Among the 44 patients with clinical stage I disease, 27 were classified as having clinical stage IA disease, and the other 17 were classified as having clinical stage IB disease. There was no significant difference in prognosis between clinical stage IA and IB disease. Similar results were obtained regarding the pathologic stage. Pathologic stage I disease showed a significantly better prognosis (Figure 3). The 5-year survivals in the 23 patients with pathologic stage IA disease and the 12 patients with stage IB disease were 73% and 67%, respectively. No significant differences in survival were observed between patients with pathologic stage IA and IB disease.

Patterns of failure. Recurrence was noted in 26 (43%) patients, and the sites of initial relapse at a median follow-up time of 65 months are shown according to the pathologic stage in Table 5. Recurrence was found in 30% of patients with stage IA disease, 25% of patients with stage IB disease, 50% of patients with stage II disease, and 67% of patients with stage IIIA disease.

Local failure was noted in 6 (10%) patients: 4 in the mediastinal lymph nodes and 2 in the bronchial stump. Locoregional recurrence tended to be found more frequently in patients with stage IIIA disease (22%) than in patients with stage I or II disease. Relapse at the bronchial stump was only seen in patients with stage IIIA disease.

Distant failure was found in 22 (36%) patients overall: 6 (26%) with stage IA disease, 2 (17%) with stage IB disease, 4 (50%) with stage II disease, and 9 (50%) with stage IIIA disease. Distant failure was most frequently noted in the brain, followed by the liver. The incidence of brain metastasis was 15% overall, 17% in patients with stage IA disease, and 11% in patients with stage IIIA disease. Bone metastasis was noted exclusively in patients with stage IIIA disease.

Discrepancy between clinical and pathologic stages. Table 6 shows the relationship between the clinical stage and the pathologic stage. Among 44 patients with clinical stage I disease, only 33 (75%) had pathologic stage I disease, and

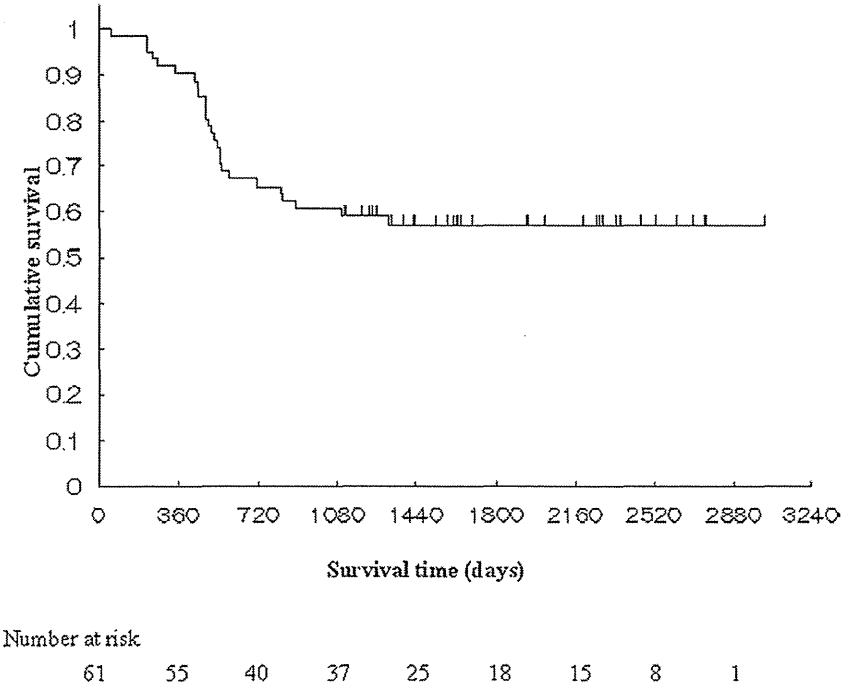

Figure 1. Survival curve for overall patients with resected SCLC.

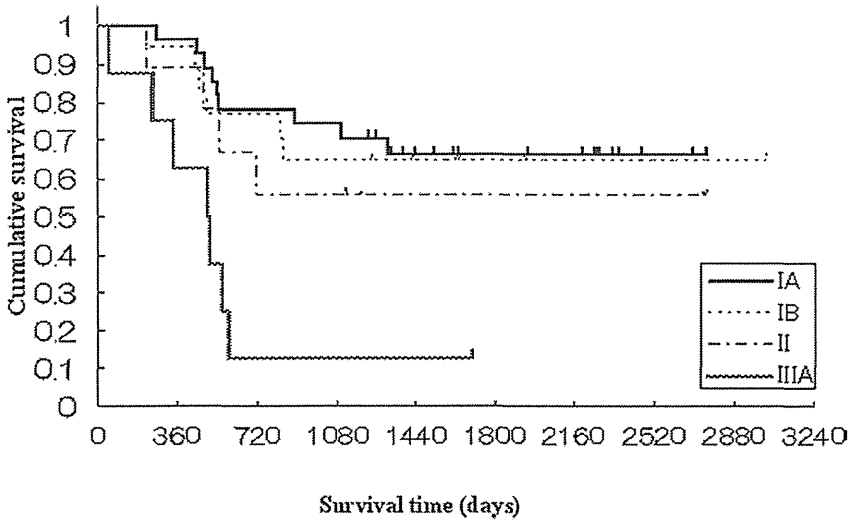

Figure 2. Survival curves for patients with resected SCLC by clinical stages.

6 had stage IIIA disease. Five patients with clinical stage IA disease had mediastinal lymph node metastasis. According to the Bowker test of symmetry, these differences were statistically significant.

Discussion

This phase II trial showed that postoperative PE for patients who underwent surgical resection of stage I to IIIA SCLC was feasible, and the outcome was acceptable. Survival was excellent in patients with stage I disease and did not appear to be inferior to that with chemoradiotherapy in patients with stage II or IIIa disease.

On the basis of the results of the British Medical Research Council, radical radiotherapy has been preferable to surgical intervention for SCLC,[17,18] and the indications for surgical resection for SCLC are still controversial. An operation would be indicated for limited SCLC because the most common relapse site after radiotherapy was locoregional, and surgical intervention might improve local control.[19] Several authors have reported that a small minority of

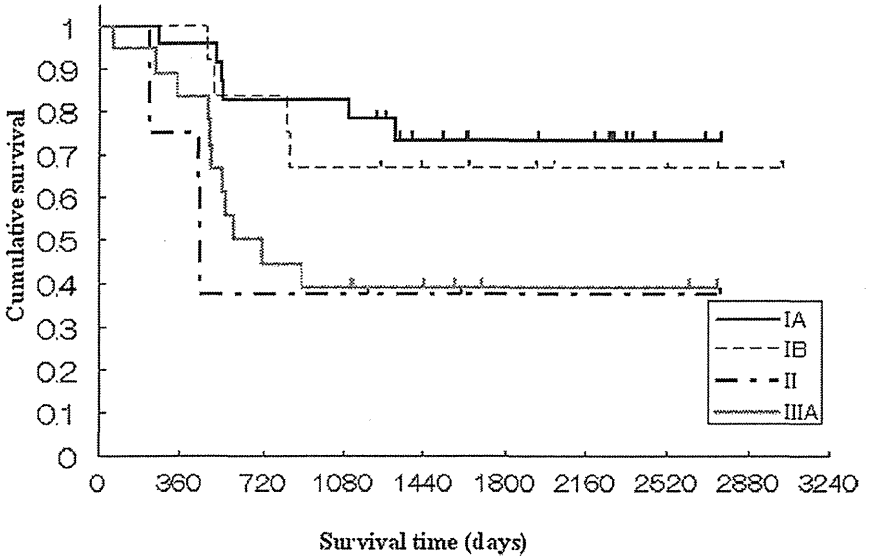

Figure 3. Survival curves for patients with resected SCLC by pathologic stage.

TABLE 5. Site of the first relapse by pathologic stages*

Variables	Overall	Stage IA	Stage IB	Stage II	Stage IIIA
No. of patients	61	23	12	8	18
No. of recurrence	26 (43%)	7 (30%)	3 (25%)	4 (50%)	12 (67%)
Recurrence					
Local					
Overall	6 (10%)	1 (4%)	1 (8%)	0 (0%)	4 (22%)
Mediastinum	4	1	1	0	2
Bronchial stump	2	0	0	0	2
Distant					
Overall	22 (36%)	6 (26%)	2 (17%)	4 (50%)	9 (50%)
Brain	9 (15%)	4 (17%)	0 (0%)	3 (38%)	2 (11%)
Bone	3	0	0	0	3
Liver	7	1	1	1	4
Lung	2	0	1	0	1
Small intestine	2	1	0	0	1

limited-stage SCLCs could be managed with an operation and postoperative chemotherapy.[1-9] According to those reports, the 5-year survivals were 28% to 36% overall and 26% to 61% in patients with stage I disease. However, most of those reports were retrospective and used various combinations of chemotherapy. Therefore, a prospective trial of adjuvant chemotherapy for patients with resected SCLC using standardized chemotherapy has been needed. Our survival data suggest that postoperative PE after major lung resection and hilar and mediastinal lymph node dissection is a feasible and promising treatment, especially for patients with stage I SCLC. The 3- and 5-year survivals for patients with stage I disease were 78% and 73%, respectively, and the median survival time was not reached. As for patients with stage II or IIIA disease, the results were not definitive, and a further prospective study is needed. This study dealt with postoperatively proved SCLC. As to the indication for surgical intervention for preoperatively diagnosed SCLC, controversies still remain. Our recommendation is as follows. When a patient has SCLC of clinical N1 or N2 status, chemoradiotherapy should be considered because a survival after an operation alone would not be good enough. Surgical intervention should be considered, however, for patients with clinical stage I disease because an operation followed by chemotherapy offers a good prognosis, as shown in this study, and because such SCLC sometimes turns out to be non-SCLC postoperatively. A phase III trial comparing chemoradiotherapy with surgical intervention followed by chemotherapy is interesting. However, the number of patients with SCLC with clinical stage I or II disease is very small, and we do not think it is possible to perform the phase III trial in this population.

TABLE 6. Relationship between clinical and pathologic stages

	Pathologic stage			
Clinical stage	I	II	IIIA	*P* value*
I	33	5	6	.011
II	1	3	5	
IIIA	1	0	7	

**P* value in Bowker's test of symmetry.

Because clinical stage and pathologic stage were significant prognostic factors in our trial, preoperative staging, intraoperative staging, or both should be a major concern for the treatment of very limited SCLC. Actually, the following preoperative investigations were performed before entry into the study in this cohort: CT scans of the chest, upper abdomen, and brain; bronchoscopy; chest plain film; radionuclide bone scans; complete blood cell count and serum chemistry; and physical examination. If the diagnosis of SCLC was made preoperatively, we recommend the same preoperative workup as done by us in this study. Furthermore, if swollen lymph nodes are detected on thoracic CT scans, we absolutely recommend mediastinoscopy for such cases. As for positron emission tomography, we have no recommendation thus far because this modality has recently begun to be evaluated, although it could be useful for staging N1 disease. Intraoperatively, hilar and mediastinal lymph node sampling or dissection was performed in 59 (97%) patients. This intraoperative staging is also important for deciding on the treatment strategy.

The site of the first relapse was another fruit of our study. This clinical trial did not use postoperative mediastinal irradiation or prophylactic cranial irradiation (PCI). We should discuss the importance of these strategies for very limited SCLC. As to locoregional recurrence, approximately 10% of the patients showed relapse in the mediastinal lymph nodes, bronchial stump, or both. Five percent of patients with stage I or II disease eventually have locore-