

carboplatin are commonly used in studies to investigate sensitizing effects.⁵²⁻⁵⁵ Of the numerous single-platinum studies, only one phase III study demonstrated the survival benefit of daily administration of cisplatin with thoracic radiotherapy. Two studies demonstrated prolonged survival with concomitant platinum-based multidrug chemotherapy and hyperfractionated radiotherapy.^{56,57} No data from large phase III studies have been reported to compare full-dose chemotherapy with low-dose sensitizing chemotherapy combined with concurrent radiotherapy for locally advanced NSCLC. CALGB conducted a phase III study to compare low-dose weekly carboplatin plus paclitaxel with concomitant radiotherapy (arm 1) and induction chemotherapy with carboplatin plus paclitaxel followed by the same concomitant chemoradiotherapy (arm 2) for stage III NSCLC.⁵⁸ Three hundred and sixty-six patients were entered in this study. The median survival on arm 1 was 11.4 months, versus 14.0 months on arm 2, and the 1-year survival rates were 48% and 54%, respectively ($P = 0.154$). The median survival achieved in each of the treatment groups was low compared to results in other recent trials. This result indicated that low-dose weekly carboplatin plus paclitaxel with concomitant radiotherapy might be insufficient treatment for stage III NSCLC.

The Southwest Oncology Group (SWOG) conducted a phase II study of concurrent chemoradiotherapy with cisplatin plus etoposide followed by consolidation docetaxel in stage IIIB NSCLC.⁵⁹ Treatment consisted of cisplatin 50-mg/m² on days 1, 8, 29, and 36; etoposide 50-mg/m² on days 1 through 5 and 29 through 33; and concurrent thoracic radiotherapy, for a total dose of 61-Gy. Consolidation docetaxel was started 4 to 6 weeks after chemoradiotherapy, at an initial dose of 75-mg/m². Eighty-three eligible patients were entered in this study. The median survival was 26 months, and the 1-, 2-, and 3-year survival rates were 76%, 54%, and 37%, respectively.⁵⁹ These results were much better than the results of the previous SWOG trial. Phase III trials evaluating docetaxel consolidation have been initiated to validate these results.

Future directions

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, such as gefitinib (ZD1839) and erlotinib (OSI-774), are some one of the most promising target-based agents for NSCLC.⁶⁰⁻⁶² EGFR tyrosine kinase inhibitors have shown encouraging antitumor activity for NSCLC in phase II studies. Moreover, it has been reported that gefitinib potentiated the efficacy of radiotherapy in human colorectal cancer and human squamous cell carcinoma in head and neck xenograft models.⁶³⁻⁶⁷ Thus, the combination of gefitinib with chemoradiotherapy is a candidate strategy to improve the survival of patients with unresectable locally advanced NSCLC. The JCOG has started a safety and efficacy trial of cisplatin and vinorelbine followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced NSCLC (JCOG 0402-MF).

Chemoradiotherapy for small cell lung cancer

Patient selection

SCLC is generally classified into two stages, LD and ED.^{68,69} In the consensus reports of the International Association of Lung Cancer (IASLC), LD is defined as disease involvement of one hemithorax, including ipsilateral pleural effusion and regional lymph nodes, including the ipsilateral hilar, bilateral mediastinal, and bilateral supraclavicular nodes.⁶⁸ Patients with LD-SCLC, except for those with ipsilateral malignant pleural effusion and ipsilateral pulmonary metastasis, are considered to be candidates for chemoradiotherapy. Patients requiring radiotherapy with a radiation field of more than half of the lung, or those with preexistent pulmonary fibrosis identified on plain chest X-ray film, should be excluded from chemoradiotherapy.^{16,17}

Standard chemoradiotherapy for small cell lung cancer

A meta-analysis including 13 trials and 2140 patients with LD-SCLC demonstrated the survival benefit of chemoradiotherapy as compared with chemotherapy alone.⁷⁰ The relative risk of death in the chemoradiotherapy group as compared with the chemotherapy group was 0.86 (95% CI, 0.78 to 0.94; $P = 0.001$), corresponding to a 14% reduction in the mortality rate. The benefit in terms of overall survival at 3 years was 5.4%. Based on this meta-analysis, chemoradiotherapy is considered to be the standard treatment for LD-SCLC. In this meta-analysis, non-platinum-based combination chemotherapies were commonly used, and only a few trials used platinum-based modern chemotherapy. Cisplatin plus etoposide is now widely regarded as the standard chemotherapy for LD-SCLC, particularly because this regimen can be integrated with concurrent thoracic irradiation, with acceptable toxicity.⁷¹ Early thoracic irradiation with concurrent cisplatin-plus-etoposide chemotherapy is the state-of-the-art treatment for LD-SCLC.

A United States intergroup trial demonstrated the survival benefit of twice-daily accelerated thoracic radiotherapy over once-daily radiotherapy with cisplatin plus etoposide for LD-SCLC¹⁰ (Table 3). Four hundred and seventeen LD-SCLC patients were randomized to receive a total of 45-Gy of concurrent thoracic radiotherapy, given either twice daily over a 3-week period or once daily over a period of 5 weeks. The median survival was 19 months for the once-daily group and 23 months for the twice-daily group. The 2-year and 5-year survival rates for patients receiving once-daily radiotherapy were 41% and 16%, and these rates for the twice-daily group were 47% and 26% ($P = 0.04$ by log-rank test).¹⁰ In contrast, another phase III trial, using split-course twice-daily radiotherapy, failed to demonstrate a survival benefit of twice-daily over once-daily radiotherapy with cisplatin plus etoposide.^{72,73} A split schedule of radiotherapy seemed to diminish the benefit of twice-daily radiotherapy (Table 3).

The brain is one of the most common sites of relapse of SCLC. However, the central nervous system is protected

Table 3. Twice-daily versus once-daily radiotherapy for LD-SCLC

Author	Chemotherapy	Radiotherapy	n	MST (Months)	5-Year Survival	P Value
Turrisi ¹⁰	CDDP + ETOP × 4	1.5 Gy × 2/Day, 45 Gy, 1st cycle, continuous	211	23	26%	P = 0.04
	CDDP + ETOP × 4	1.8 Gy/Day, 45 Gy, 1st–2nd cycles, continuous	206	19	16%	
Bonner ⁷² Schild ⁷³	CDDP + ETOP × 6	1.5 Gy × 2/Day, 48 Gy, 4th–5th cycles, split	130	20.6	22%	P = 0.68
	CDDP + ETOP × 6	1.8 Gy/Day, 50.4 Gy, 4th–5th cycles, continuous	132	20.6	21%	

CDDP, cisplatin; ETOP, etoposide

from anticancer drugs by the blood-brain barrier. Several phase III trials have demonstrated that prophylactic cranial irradiation (PCI) reduces the incidence of brain metastasis in patients with SCLC, but no phase III trials have demonstrated a survival benefit of PCI for patients with SCLC.^{74–76}

A meta-analysis, using individual data on 987 patients with SCLC in complete remission (CR) who took part in seven trials that compared PCI with no PCI demonstrated a survival benefit of PCI.⁷⁷ The relative risk of death in the PCI group as compared with the no-PCI group was 0.84 (95% CI, 0.73 to 0.97; $P = 0.01$), which corresponds to a 5.4% increase in the rate of survival at 3 years (15.3% in the no-PCI group vs 20.7% in the PCI group). This absolute improvement in 3-year survival (5.4%) was the same as that shown in a meta-analysis comparing chemotherapy with chemoradiotherapy for SCLC.^{70,77} Thus, PCI for SCLC, in patients who have achieved a complete response (CR), has a power to improve survival similar to that of thoracic radiotherapy for LD-SCLC.

The state-of-the-art treatment for LD-SCLC is considered to be four cycles of combination chemotherapy with cisplatin plus etoposide, combined with early concurrent twice-daily thoracic irradiation (45 Gy). If patients achieve a CR, PCI should be administered. A 5-year survival rate of approximately 25% is expected with the state-of-the-art treatment for LD-SCLC.

Future directions

The JCOG conducted a randomized multicenter phase III study of irinotecan plus cisplatin versus etoposide plus cisplatin for previously untreated patients with ED-SCLC (JCOG 9511).⁸ One hundred and fifty-four patients were randomized, 77 into each arm. The median survival time was 12.8 months in the irinotecan-plus-cisplatin arm and 9.4 months in the etoposide-plus-cisplatin arm. The irinotecan-plus-cisplatin arm showed significantly better survival compared with standard treatment with etoposide plus cisplatin ($P = 0.002$; unadjusted one-sided log-rank test). Treatment with four cycles of irinotecan plus cisplatin every 4 weeks in ED-SCLC patients yielded a highly significant improvement in survival, with less myelosuppression, over the standard etoposide plus cisplatin.⁸ Thus, the incorporation of

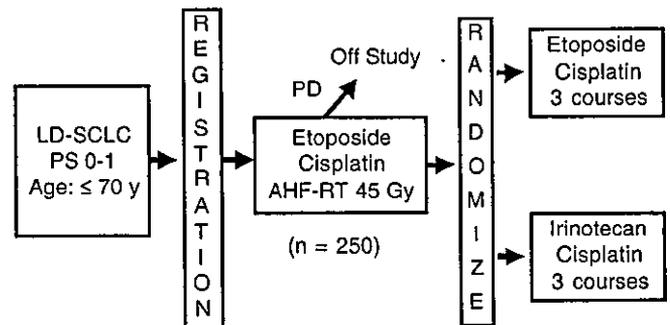


Fig. 1. Ongoing randomized phase III trial in patients with limited-stage small cell lung cancer (LD-SCLC) by Japan Clinical Oncology Group (JCOG; JCOG 0202MF). PS, performance status; PD, progressive disease; AHF-RT, accelerated hyperfractionated radiotherapy

irinotecan into the treatment for LD-SCLC is considered to be one of the most important strategies for improving the survival of LD-SCLC patients. Concurrent twice-daily thoracic radiotherapy with combination chemotherapy consisting of irinotecan and cisplatin may be the most powerful treatment for LD-SCLC patients if it is possible to use the full dose of irinotecan with acceptable toxicity. Previously, the JCOG conducted a dose-finding study of irinotecan and cisplatin plus concurrent radiotherapy for unresectable stage III NSCLC (JCOG 9405).³² The dose intensity of irinotecan in the study was low, because of the need to omit irinotecan administration on days 8 and/or 15 as a result of leukopenia or diarrhea, and the radiotherapy completion rate was also low. This was a very small study, however, and chemotherapy with full-dose irinotecan and cisplatin plus concurrent radiotherapy was deemed unacceptable based on the results of the JCOG 9405 study. Full-dose chemotherapy consisting of etoposide and cisplatin can be used in combination with concurrent radiotherapy. However, when irinotecan is used as a single agent with concurrent radiotherapy, the dose of irinotecan must be reduced from 100 mg/m² to 60 mg/m² in a weekly schedule.⁷⁸ This dose reduction of irinotecan likely reduces the efficacy of irinotecan in the treatment of LD-SCLC patients. The JCOG is conducting a phase III study (JCOG 0202-MF) of concurrent twice-daily thoracic radiotherapy with four

cycles of etoposide and cisplatin as the standard arm versus, concurrent twice-daily thoracic radiotherapy with etoposide and cisplatin, followed by three cycles of chemotherapy with the standard dose of irinotecan and cisplatin (Fig. 1).

Conclusion

Chemoradiotherapy is considered to be the standard treatment for both unresectable locally advanced NSCLC and LD-SCLC. Cisplatin-based chemotherapy with concurrent thoracic radiotherapy yields a 5-year survival rate of approximately 15% for patients with unresectable locally advanced NSCLC. Cisplatin plus etoposide with concurrent twice-daily thoracic radiotherapy yields a 5-year survival rate of approximately 25% for patients with LD-SCLC. Several new strategies are currently underway to investigate improvements in survival for these patients. The incorporation of target-based drugs, such as gefitinib, is considered to be the most promising strategy for unresectable locally advanced NSCLC. The incorporation of irinotecan is also a promising strategy to improve the survival of patients with LD-SCLC. The JCOG is presently conducting clinical trials to develop a new strategy for the treatment of both unresectable locally advanced NSCLC and LD-SCLC.

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Phase I–II study of amrubicin and cisplatin in previously untreated patients with extensive-stage small-cell lung cancer

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Background: Amrubicin, a totally synthetic 9-amino-anthracycline, demonstrated excellent single-agent activity for extensive-stage small-cell lung cancer (ED-SCLC). The aims of this trial were to determine the maximum-tolerated doses (MTD) of combination therapy with amrubicin and cisplatin, and to assess the efficacy and safety at their recommended doses (RD).

Patients and methods: Eligibility criteria were patients having histologically or cytologically proven measurable ED-SCLC, no previous systemic therapy, an Eastern Cooperative Oncology Group performance status of 0–2 and adequate organ function. Amrubicin was administered on days 1–3 and cisplatin on day 1, every 3 weeks.

Results: Four patients were enrolled at dose level 1 (amrubicin 40 mg/m²/day and cisplatin 60 mg/m²) and three patients at level 2 (amrubicin 45 mg/m²/day and cisplatin 60 mg/m²). Consequently, the MTD and RD were determined to be at level 2 and level 1, respectively. The response rate at the RD was 87.8% (36/41). The median survival time (MST) was 13.6 months and the 1-year survival rate was 56.1%. Grade 3/4 neutropenia and leukopenia occurred in 95.1% and 65.9% of patients, respectively.

Conclusions: The combination of amrubicin and cisplatin has demonstrated an impressive response rate and MST in patients with previously untreated ED-SCLC.

Key words: anthracycline, cisplatin, phase I–II, small-cell lung cancer

Introduction

Small-cell lung cancer (SCLC) is one of the most chemosensitive solid tumors, and the outcome of SCLC patients is slowly but surely improving. Combination chemotherapy consisting of cisplatin plus etoposide and concurrent twice-daily thoracic radiotherapy has yielded a 26% 5-year survival rate in limited-stage (LD) patients [1]. Despite the high response rate to combination chemotherapy, however, local and distant failure is very common, especially in extensive-stage (ED) patients. Moreover, resistance to chemotherapeutic agents develops easily after failure of initial treatment. Thus, long-term survivors are still very rare among patients with ED-SCLC. To improve the outcome of SCLC patients, several strategies,

such as high-dose chemotherapy, dose-intensive chemotherapy, alternating chemotherapy and introduction of new drugs, have been investigated [2–6]. However, only the introduction of new agents has improved the outcome of SCLC patients. Combination chemotherapy with etoposide plus cisplatin or etoposide plus cisplatin alternating cyclophosphamide, doxorubicin and vincristine had been mainly used for SCLC in North America. Recently, a Japanese trial [Japan Clinical Oncology Group (JCOG) 9511] demonstrated the superiority of the combination of irinotecan and cisplatin for ED-SCLC patients over the combination of etoposide and cisplatin [6]. The development of more active chemotherapy, and especially the introduction of effective new drugs, is therefore essential to improve the survival of SCLC patients.

Amrubicin (SM-5887) is a totally synthetic anthracycline and a potent topoisomerase II inhibitor [7–14]. It has antitumor activity, and is more potent than doxorubicin against various mouse experimental tumors and human tumor

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xenografts. Amrubicin and its 13-hydroxy metabolite, amrubicinol, inhibit purified human DNA topoisomerase II [11]. Amrubicinol is 10–100 times more cytotoxic than amrubicin [9]. The potent therapeutic activity of amrubicin is caused by the selective distribution of its highly active metabolite, amrubicinol, in tumors [9]. In an experimental animal model, amrubicin did not exhibit any chronic cardiotoxicity potential, and no deleterious effects on doxorubicin-induced cardiotoxicity in dogs was observed [14]. In a phase II study of amrubicin using a schedule of 45 mg/m² on days 1–3 every 3 weeks, in 33 previously untreated ED-SCLC patients, an overall response rate of 76% and a complete response (CR) rate of 9% were reported [15]. Moreover, median survival time (MST) was 11.7 months in the single-agent phase II study of amrubicin. Amrubicin is one of the most active new agents for SCLC. Thus, we conducted a phase I/II study of amrubicin plus cisplatin for untreated ED-SCLC, because cisplatin is considered as one of the most important drugs in the treatment of SCLC. The aims of this trial were to determine the maximum-tolerated doses (MTD) of combination therapy of amrubicin with cisplatin, to assess the efficacy and safety for ED-SCLC at their recommended doses (RD), and to examine the pharmacokinetics of the drug combination.

Patients and methods

Patient selection

Patients with histologically and/or cytologically documented SCLC were eligible for this study. Each patient was required to meet the following criteria: extensive-stage disease [16]; no prior therapy for primary lesion; measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; expected survival time >2 months; age 20–74 years; adequate hematological function [white blood cell (WBC) count 4000–12 000/mm³, neutrophils ≥2000/mm³, platelets ≥100 000/mm³, hemoglobin ≥10 g/dl]; adequate hepatic function [total bilirubin within 1.5× the upper limit of normal; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within 2.5× the upper limit of normal]; adequate renal function (creatinine within the upper limit of normal); partial pressure of arterial oxygen 60 torr; no abnormality requiring treatment on electrocardiogram; left ventricle ejection fraction >60%; written informed consent. Patients with symptomatic brain metastasis, pleural effusion that required drainage, non-steroidal anti-inflammatory drug or glucocorticoid use for >50 days, pericarditis carcinomatous, active infection, varicella, superior vena cava syndrome, syndrome of inappropriate secretion of anti-diuretic hormone (SIADH), gastric and/or duodenal ulcer, severe heart disease, severe renal disease, active concomitant malignancy, symptomatic pneumonitis and/or pulmonary fibrosis and pregnant/nursing women were excluded. This study was approved by the Institutional Review Board at each hospital.

Patient evaluation

Pretreatment evaluation consisted of complete blood cell counts, differential, routine chemistry measurements, progastrin-releasing peptide (ProGRP), neuron-specific enolase, electrocardiogram, echocardiography, chest radiograph, chest and abdominal computed tomography (CT) scan, whole-brain magnetic resonance imaging (MRI) or CT scan, and isotope bone scan. Complete blood cell counts, differential and routine chemistry measurements were performed at least once a week during the chemotherapy.

Treatment schedule

At level 1, chemotherapy consisted of cisplatin 60 mg/m² on day 1 and amrubicin 40 mg/m² on days 1–3. Amrubicin was administered as an intravenous injection over 5 min and cisplatin was administered as a drip infusion over 60–120 min with adequate hydration. At level 2 the dose of amrubicin was increased to 45 mg/m² on days 1–3. Level 3 was planned with cisplatin 80 mg/m² on day 1 and amrubicin 45 mg/m² on days 1–3. The chemotherapy was repeated every 3 weeks for four to six courses. Inpatient dose escalation was not allowed. Administration of granulocyte colony-stimulating factor (G-CSF) was permitted prophylactically for patients expected to experience grade 3 neutropenia during the first course. Prophylactic administration of G-CSF was only permitted at second or later courses.

The administrations of both cisplatin and amrubicin were postponed if patients met the following criteria: WBC <3000/mm³; neutrophils <1500/mm³; platelets <100 000/mm³; AST and ALT >5× the upper limit of normal; total bilirubin >1.5× the upper limit of normal; creatinine >1.3× the upper limit of normal; ECOG PS 3 or 4; active infection; grade 2 or worse non-hematological toxicity, except for alopecia, anorexia, nausea, vomiting or fatigue.

The administrations of both cisplatin and amrubicin were withdrawn if patients met the following criteria: tumor regression <15% after first course or <30% after second course; WBC <3000/mm³; neutrophils <1500/mm³; platelets <100 000/mm³; no recovery from grade 3 or 4 non-hematological toxicity at 6 weeks after the start of previous chemotherapy; abnormality of electrocardiogram requiring treatment for more than 6 weeks; left ventricle ejection fraction <48%; treatment delay of >4 weeks.

The dose of amrubicin was decreased 5 mg/m²/day if patients met the following criteria: grade 4 leukopenia or neutropenia for ≥4 days; grade 3 neutropenia with fever; platelets <20 000/mm³ during the previous course. The dose of cisplatin was decreased to 75% if creatinine increased to >1.5× the upper limit of normal during the previous course.

The dose-limiting toxicity (DLT) was defined as follows: grade 4 leukopenia or neutropenia for ≥4 days; grade 3 febrile neutropenia; platelets <20 000/mm³; grade 3 or worse non-hematological toxicity except for nausea, vomiting, anorexia, fatigue, hyponatremia and infection. Initially, three patients were treated at each dose level. If DLT was not observed in any of the three patients, dose escalation was carried out. If DLT was observed in one of three patients, an additional three patients were entered at the same dose level. If DLT was observed in three or more of six patients, or two or three of the initial three patients, we considered that dose to be the MTD. If DLT was observed in one or two of six patients, dose escalation was also carried out. Dose escalation was determined based only on the data from the first course of chemotherapy.

Response and toxicity evaluation

Response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) and tumor markers were excluded from the criteria [17]. CR was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks and no new lesions. Partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameters of target lesion, taking as reference the baseline sum longest diameter, the required non-progression in non-target lesions and no new lesions for at least 4 weeks. Stable disease (SD) included: regression of target lesions insufficient to meet the criteria for PR, a <20% increase in the sum of the longest diameter of target lesion, taking as reference the smallest sum longest diameters recorded since the treatment started, the required non-progression in non-target lesions and no new lesions for at least 6 weeks. Progressive disease (PD) indicated a >20% increase in the sum of the longest diameters of target lesion, taking as reference the smallest sum longest diameter recorded since the treatment started

and/or unequivocal progression of existing non-target lesions and/or appearance of new lesions. The evaluation of objective tumor response for all patients was performed by an external review committee.

Toxicity grading criteria of the National Cancer Institute Common Toxicity Criteria (version 2.0) was used for evaluation of toxicity.

Statistical analysis

This study was designed to reject response rates of 70% (P0) at a significance level of 0.05 (one-tailed) with a statistical power of 80% to assess the activity of the regimen as a 85% response rate (P1) at the recommended dose. The upper limit of rejection was 29 responses (CR + PR) among 37 evaluable patients. Overall survival was defined as the interval between the first administration of the drugs in this study and death or the

last follow-up visit. Median overall survival was estimated using the Kaplan-Meier method [18].

Pharmacokinetic analysis

Pharmacokinetic analysis was performed in patients entering the phase I section of this study. One milliliter of the blood was taken from the patients before administration of amrubicin, and at 0 min, 15 min, 1, 2, 3, 4, 8 and 24 h after administration on days 1 and 3 in the first course of chemotherapy. Concentrations of amrubicin and its active metabolite, amrubicinol, in plasma and red blood cells were measured as reported elsewhere [9].

Results

Patient characteristics

Between April 2001 and December 2002, 45 patients with ED-SCLC were enrolled and 44 were treated in this study (Table 1). One patient did not receive the protocol treatment because atrial fibrillation was observed just before administration on day 1 of the first course. All treated patients were assessed for response, survival and toxicity. The median age of the treated patients was 64.5 years (range 50–74). There were 36 males and eight females. Five patients had an ECOG PS 0 and 39 patients had PS 1. Only one patient received surgery for brain metastasis as a prior therapy.

MTD and DLT in the phase I study

Four patients were enrolled at dose level 1 (amrubicin 40 mg/m² on days 1–3 and cisplatin 60 mg/m² on day 1) and three patients at level 2 (amrubicin 45 mg/m² on days 1–3 and cisplatin 60 mg/m² on day 1). Toxicities in the phase I study are listed in Table 2. No DLT were observed during the first course of level 1. At level 2, grade 4 neutropenia for ≥4 days and febrile neutropenia occurred in one patient, and febrile neutropenia and grade 3 constipation occurred in another patient. Consequently, the MTD and RD were determined to be level 2 and level 1, respectively.

Pharmacokinetics of amrubicin and its active metabolite, amrubicinol

Pharmacokinetic parameters of amrubicin in plasma were almost identical on days 1 and 3 at the two dose levels (Table 3). No clear dose relationship in the area under the concentration–time curve (AUC) of amrubicin in the plasma was observed. The AUC of amrubicinol in red blood cells tended to increase on day 3 at both doses (Table 4). No clear dose relationship in the AUC of amrubicinol in red blood cells was observed. Combination with cisplatin did not alter the pharmacokinetics of amrubicin and amrubicinol (data not shown).

Treatment received in patients treated at the RD

Forty-one patients were treated at the RD: amrubicin 40 mg/m² on days 1–3 and cisplatin 60 mg/m² on day 1. Of 41 patients, 32 (78%) patients received more than three

Table 1. Characteristics of treated patients

	Phase I	Phase II	Total
Number of patients	7	37	44
Gender			
Male	5	31	36
Female	2	6	8
Age (years)			
Median	65	64	64.5
Range	54–73	50–74	50–74
ECOG PS			
0	0	5	5
1	7	32	39
2	0	0	0
Stage			
IIIB	0	2	2
IV	7	35	42
Prior therapy			
Yes	0	1	1
No	7	36	43
Serum ALP			
Normal	7	29	36
Elevated	0	7	7
Serum LDH			
Normal	3	14	17
Elevated	4	23	27
Na			
Normal	6	35	41
Decreased	1	2	3
Number of metastases			
0	0	2	2
1	4	27	31
2	3	6	9
3	0	1	1
4 or more	0	1	1

In one patient, serum ALP level could not be measured. ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ALP, alkaline phosphatase.

Table 2. Toxicities during the first course in the phase I study

	Level 1 (n=4)					Level 2 (n=3)				
	40 mg/m ² days 1-3					45 mg/m ² days 1-3				
	60 mg/m ² day 1					60 mg/m ² day 1				
	Grade (NCI CTC)					Grade (NCI CTC)				
	0	1	2	3	4	0	1	2	3	4
Amrubicin										
Cisplatin										
Leukopenia	0	1	1	2	0	0	0	1	1	1
Neutropenia	0	0	0	2	2	0	0	0	0	3
Febrile neutropenia	4	-	-	0	0	1	-	-	2	0
Hemoglobin	1	1	2	0	0	2	1	0	0	0
Thrombocytopenia	1	2	0	1	0	0	2	0	1	0
Stomatitis	3	0	1	0	0	3	0	0	0	0
Nausea	1	1	2	0	-	1	1	0	1	-
Constipation	3	0	1	0	0	1	0	1	1	0
Hyponatremia	2	1	0	0	1	1	2	0	0	0
Hypocalcemia	3	0	1	0	0	3	0	0	0	0

Dose limiting toxicity at level 2: febrile neutropenia, two patients; grade 4 neutropenia ≥ 4 days, one patient; grade 3 constipation, one patient. NCI CTC, National Cancer Institute Common Toxicity Criteria.

Table 3. Pharmacokinetics of amrubicin in plasma

Dose	n	Day	$T_{1/2\alpha}$ (h)	$T_{1/2\beta}$ (h)	V_d (l)	CL (l/h)	AUC _{0-24h} (ng h/ml)
40 mg/m ²	4	1	0.11 \pm 0.04	2.29 \pm 0.31	46.6 \pm 11.0	13.6 \pm 1.8	2995 \pm 434
	4	3	0.08 \pm 0.01	2.89 \pm 0.34	50.0 \pm 10.6	11.6 \pm 1.9	3511 \pm 514
45 mg/m ²	3	1	0.13 \pm 0.05	2.39 \pm 0.34	56.3 \pm 10.6	14.9 \pm 1.8	3052 \pm 402
	3	3	0.09 \pm 0.03	2.27 \pm 0.18	51.9 \pm 3.7	14.2 \pm 2.3	3217 \pm 479

$T_{1/2\alpha}$, half-life at distribution phase; $T_{1/2\beta}$, half-life at elimination phase; V_d , volume of distribution; CL, clearance; AUC, area under the concentration-time curve.

courses of chemotherapy, and 10 (31%) of these 32 patients needed dose reduction of amrubicin at the fourth course (Table 5). Of 41 patients, 22 (54%) patients completed four courses of chemotherapy without dose modification. The main cause of dose reduction was myelosuppression, especially leukopenia and neutropenia.

Objective tumor response and overall survival

The objective tumor responses are given in Table 6. Four CRs and 32 PRs occurred, for an objective response rate of 87.8% [95% confidence interval (CI) 73.8% to 95.9%] in 41 patients treated at the RD. The objective response rate for all 44 patients was 88.6% (95% CI 75.4% to 96.2%). The overall survival times of the 41 patients treated at the RD are shown in Figure 1. The MST of the 41 patients was 13.6 months (95% CI 11.1-16.6), with a median follow-up time for eight censored patients of 16.4 months (95% CI 14.2-18.8). The 1- and 2-year survival rates were 56.1% and 17.6%, respectively. The MST of all 44 patients was 13.8 months (95% CI 11.1-16.6). The 1- and 2-year survival rates of all 44 patients were 56.8% and 21.4%, respectively.

Table 4. Pharmacokinetics of amrubicin in red blood cells

Dose	n	Day	$T_{1/2}$ (h)	AUC _{0-24h} (ng-h/ml)
40 mg/m ²	4	1	21.0 \pm 3.1	1412 \pm 314
	4	3	20.7 \pm 4.8	2159 \pm 622
45 mg/m ²	3	1	19.6 \pm 6.1	1098 \pm 277
	3	3	18.1 \pm 5.7	2027 \pm 332

$T_{1/2}$, elimination half-life; AUC, area under the concentration-time curve.

Table 5. Treatment received in patients treated at the recommended dose

Cycle	n	Amrubicin (mg/m ²)			Cisplatin (mg/m ²)	
		40	35	30	60	45
1	41	41			41	
2	36	30	6		36	
3	33	26	5	2	33	
4	32	22	8	2	32	
5	18	9	5	4	18	
6	13	6	3	4	12	1

Table 6. Response rates

	n	CR	PR	SD	PD	NE	Response rate (%) (95% CI)
All	44	4	35	3	0	2	88.6 (75.4–96.2)
Treated at RD	41	4	32	3	0	2	87.8 (73.8–95.9)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; 95% CI, 95% confidence interval; RD, recommended dose.

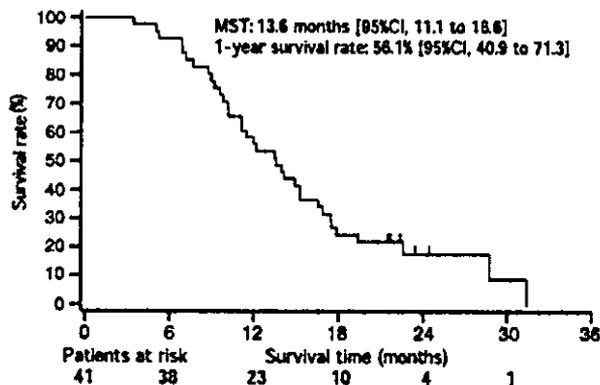


Figure 1. Overall survival of patients with extensive-stage small-cell lung cancer who were treated with amrubicin and cisplatin at the recommended dose. MST, median survival time; 95% CI, 95% confidence interval.

Toxicity in patients treated at the RD

The worst grades of hematological and non-hematological toxicities experienced by each patient are listed in Table 7. Hematological toxicity, especially leukopenia and neutropenia, was common and relatively severe. Grade 3 or worse leukopenia and neutropenia occurred in 65.9% and 95.1% of patients, respectively. Febrile neutropenia was observed in two patients at level 2. Grade 3 or worse anemia and thrombocytopenia occurred in 53.7% and 24.4% of patients, respectively. Four patients received platelet transfusions. Common non-hematological toxicities were gastrointestinal toxicity, such as anorexia, nausea, vomiting, constipation, diarrhea and stomatitis. Gastric ulcers developed in three patients. Hepatic and renal toxicity were not common in this study. Grade 3 or worse hyponatremia and hypokalemia occurred in 22% and 9.8% of patients, respectively. One patient developed myocardial infarction; however, cardiac toxicity was not common. No treatment-related deaths were observed.

Discussion

Doxorubicin and epirubicin are classified as active agents for SCLC, for which single-agent activity is a >20% response rate [19]. Doxorubicin has been used as a constituent of combination therapy for SCLC in the CAV (cyclophosphamide, doxorubicin and vincristine) and CAP (cyclophosphamide, doxorubicin and cisplatin) regimens. Epirubicin has shown

Table 7. Toxicity in patients treated at the recommended dose (n=41)

	Grade (NCI CTC)					Grade 3/4 (%)
	0	1	2	3	4	
Leukopenia	1	0	13	20	7	65.9
Neutropenia	0	1	1	7	32	95.1
Febrile neutropenia	41	–	–	0	0	0.0
Hemoglobin	1	8	10	17	5	53.7
Thrombocytopenia	9	14	8	10	0	24.4
Stomatitis	22	13	5	1	0	2.4
Anorexia	1	14	13	13	0	31.7
Nausea	3	15	14	9	0	22.0
Vomiting	20	8	11	2	0	4.9
Constipation	24	1	13	3	0	7.3
Diarrhea	26	12	1	2	0	4.9
Gastric ulcer	38	0	1	2	0	4.9
Bilirubin	24	12	4	1	0	2.4
Hyponatremia	18	14	–	7	2	22.0
Hypokalemia	31	6	–	4	0	9.8
Hyperkalemia	33	3	4	1	0	2.4
Hypocalcemia	31	5	4	0	1	2.4

NCI CTC, National Cancer Institute Common Toxicity Criteria.

50% and 48% response rates in two clinical studies in 41 and 80 previously untreated patients, respectively, with ED-SCLC [20, 21]. However, currently, combination modalities containing doxorubicin or epirubicin are not being used in the therapy of SCLC, in preference to combination therapy with cisplatin and etoposide. Since amrubicin has shown excellent single-agent activity [15], it can be expected to be superior to other anthracyclines in the treatment of SCLC. Additionally, the present results of combination therapy with cisplatin support the view that amrubicin may be a promising agent that overcomes the therapeutic plateau of SCLC.

Amrubicin is one of the most promising new agents for the treatment of SCLC. In a previous phase II study of amrubicin 45 mg/m² on days 1–3 every 3 weeks as a monotherapy for chemo-naïve ED-SCLC, a 76% overall response rate and 11.7 month MST were observed [15]. The overall response rate and MST were comparable to those achieved with standard combination chemotherapy, such as etoposide plus cisplatin [5, 6]. Moreover, only a few patients treated in the phase II study received salvage chemotherapy consisting of cisplatin and etoposide [15]. The major toxicity of amrubicin as a monotherapy was hematological toxicity: grade 4 leukopenia and neutropenia were seen in 12.1% and 39.4% of patients, respectively, and thrombocytopenia and anemia of grade 3 or worse in 21.2%. Hepatic, renal and cardiac toxicities with amrubicin were not common. Cisplatin is a key drug for the treatment of SCLC and its hematological toxicity, such as leukopenia and neutropenia, is not severe. Thus, we conducted a phase I–II study of amrubicin and cisplatin treatment for chemo-naïve ED-SCLC to determine the MTD of this combination therapy, to

assess the efficacy and safety of the drugs delivered at their RD in chemo-naïve ED-SCLC, and to examine pharmacokinetics.

The topoisomerase I inhibitor, irinotecan, is also very effective for SCLC [6]. Combinations of topoisomerase I and topoisomerase II inhibitors, such as irinotecan plus etoposide, have been reported as active combination chemotherapy for SCLC [22]. Thus, combination of irinotecan and amrubicin is another candidate for new combination chemotherapy for SCLC. A phase I study of irinotecan and amrubicin for chemo-naïve non-SCLC was performed in National Cancer Center Hospital (unpublished data). However, the MTD was less than irinotecan 60 mg/m² on days 1 and 8 and amrubicin 35 mg/m² on days 2–4, due to relatively severe myelotoxicity. We considered that amrubicin <35 mg/m² on days 2–4 with irinotecan 60 mg/m² on days 1 and 8 was insufficient to treat SCLC.

In this study, we determined the RD to be amrubicin 40 mg/m² on days 1–3 and cisplatin 60 mg/m² on day 1 every 3 weeks, and 41 patients were treated at the RD. Main toxicities of this combination chemotherapy were myelosuppression, especially leukopenia and neutropenia, and gastrointestinal toxicities including anorexia, nausea, vomiting, constipation, diarrhea, stomatitis and gastric ulcer. Of 41 patients, 32 (78%) patients received four or more courses of chemotherapy, and 22 (54%) patients completed four courses of chemotherapy without dose modification. One patient developed myocardial infarction; however, other cardiac toxicity, including decrease in left ventricle ejection fraction, was not observed in up to six courses of chemotherapy. The total dose of amrubicin was 720 mg/m². Grade 3 or 4 hyponatremia occurred in nine (22%) patients; however, most of the patients were asymptomatic. No unexpected toxicities and no treatment-related deaths were observed in this study. Toxicities observed in this study were manageable.

Four CRs and 32 PRs occurred, for an objective response rate of 87.8% (95% CI 73.8% to 95.9%) in 41 patients treated at the RD. In most patients, ProGRP levels changed in parallel with tumor responses. The MST of the 41 patients was 13.6 months, and the 1-year survival rate was 56.1%. These results were better than recently reported results for irinotecan and cisplatin in chemo-naïve ED-SCLC: an objective response rate of 84% and MST of 12.8 months [6]. The combination of amrubicin and cisplatin has demonstrated an impressive response rate and MST in patients with previously untreated ED-SCLC. A possible reason for the better results is over-selection of patients, because we used unusual exclusion criteria such as non-steroidal anti-inflammatory drug or adrenal cortical steroid use for >50 days, and gastric and/or duodenal ulcer. However, in a phase II study, this kind of bias is not uncommon.

Combination chemotherapy with etoposide plus cisplatin or etoposide plus cisplatin, alternating with cyclophosphamide, doxorubicin and vincristine, had been considered as standard chemotherapy for SCLC in North America and Japan. A Japanese phase III trial (JCOG 9511) demonstrated that treatment with four cycles of irinotecan plus cisplatin every 4 weeks yielded a highly significant improvement in survival in

ED-SCLC patients over standard etoposide plus cisplatin, with less myelosuppression [6]. Based on the results of the JCOG 9511 trial, irinotecan plus cisplatin is considered to be the reference chemotherapy arm for ED-SCLC in future trials in Japan [23]. The JCOG are preparing a phase III clinical trial of amrubicin and cisplatin for previously untreated ED-SCLC to compare combination therapy of irinotecan with cisplatin.

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CLINICAL INVESTIGATION

Lung

A PHASE II STUDY OF HYPERFRACTIONATED ACCELERATED
RADIOTHERAPY (HART) AFTER INDUCTION CISPLATIN (CDDP) AND
VINORELBINE (VNR) FOR STAGE III NON-SMALL-CELL LUNG CANCER
(NSCLC)

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Purpose: The purpose was to assess the feasibility and efficacy of hyperfractionated accelerated radiotherapy (HART) after induction chemotherapy for Stage III non-small-cell lung cancer.

Methods and Materials: Treatment consisted of 2 cycles of cisplatin 80 mg/m² on Day 1 and vinorelbine 25 mg/m² on Days 1 and 8 every 3 weeks followed by HART, 3 times a day (1.5, 1.8, 1.5 Gy, 4-h interval) for a total dose of 57.6 Gy.

Results: Thirty patients were eligible. Their median age was 64 years (range, 46–73 years), 24 were male, 6 were female, 8 had performance status (PS) 0, 22 had PS 1, 9 had Stage IIIA, and 21 had Stage IIIB. All but 1 patient completed the treatment. Common grade ≥3 toxicities during the treatment included neutropenia, 25; infection, 5; esophagitis, 5; and radiation pneumonitis, 3. The overall response rate was 83%. The median survival was 24 months (95% confidence interval [CI], 13–34 months), and the 2-year overall survival was 50% (95% CI, 32–68%). The median progression-free survival was 10 months (95% CI, 8–20 months).

Conclusion: Hyperfractionated accelerated radiotherapy after induction of cisplatin and vinorelbine was feasible and promising. Future investigation employing dose-intensified radiotherapy in combination with chemotherapy is needed. © 2005 Elsevier Inc.

Non-small-cell lung cancer, Hyperfractionated accelerated radiation therapy, Chemoradiotherapy.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death for men and the second for women in Japan. During 2001, approximately 55,000 patients died of lung and bronchus cancer (1). Surgery is the standard of care for patients with Stage I–II non-small-cell lung cancer (NSCLC), but a combination of chemotherapy and thoracic radiotherapy with or without surgery is indicated for the majority of patients with Stage III disease. Cisplatin (CDDP) based chemotherapy with conventional radiotherapy improved survival compared to conventional radiotherapy alone (2–6) and was the standard of care in the 1990s. Recently, concurrent chemoradiotherapy has been revealed to be superior to sequential chemoradiotherapy (7, 8), but it is difficult to give full-dose chemotherapy using newer cytotoxic agents concurrently with radiotherapy, and the optimal combination has not yet been clarified. In the meantime, continuous hyperfractionated accelerated radiotherapy (CHART) with 3 daily fractions to intensify the local effect of

radiotherapy has been found to be superior to conventional radiotherapy (9). The survival benefit of CHART was encouraging, but the protocol including treatments on weekends and 6-h intervals between fractions had some difficulties in practicality. Mehta *et al.* introduced hyperfractionated accelerated radiotherapy (HART) (modified CHART) with 3 daily fractions and 4-h interfraction intervals with weekend breaks and also showed promising results similar to those using sequential chemoradiotherapy (10). After these results, we started a Phase II trial to evaluate the feasibility and efficacy of induction chemotherapy with HART for patients with Stage III NSCLC.

METHODS AND MATERIALS

Eligibility criteria

Eligibility criteria included previously untreated patients with pathologically proven NSCLC with clinical tumor-node-metastasis system Stage III, and pathologic N2 was also required for Stage

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IIIA; age, 20 to 74 years; performance status (PS) (based on Eastern Cooperative Oncology Group [ECOG] scale) 0 to 1; measurable disease; adequate hematologic (WBC count $\geq 4,000/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, and hemoglobin $\geq 9.5 \text{ g/dL}$), hepatic (AST and ALT level ≤ 2 times the upper limit of normal and total bilirubin level \leq the upper limit of normal), and renal (creatinine $\leq 1.2 \text{ mg/dL}$ and creatinine clearance $\geq 60 \text{ mL/min}$) functions; $\text{PaO}_2 \geq 70 \text{ torr}$; no pleural and pericardial effusion; radiation field encompassed one-half or less of the ipsilateral lung; and no serious comorbidity. All patients signed written informed consent in accordance with our institutional review board.

Pretreatment evaluation included history and physical examination; serum chemistries (lactate dehydrogenase, alkaline phosphatase, AST, ALT, bilirubin, albumin, creatinine, and calcium); chest radiograph; CT scan of the chest; ultrasound of the abdomen; MRI or CT scan of the brain; and bone scintigraphy.

Treatment details

The treatment consisted of 2 cycles of CDDP 80 mg/m^2 on Day 1 and vinorelbine (VNR) 25 mg/m^2 on Days 1 and 8 every 3 weeks followed by HART; 3 times a day with minimal interval of 4 hours for a total dose of 57.6 Gy in 36 fractions over 2.5 weeks.

Radiation therapy was started after the patient recovered from the toxicity of chemotherapy and was delivered with megavoltage equipment. Lung heterogeneity corrections were not used. The first and third fraction of each day consisted of anterior-posterior opposed fields that encompassed the primary tumor, the metastatic lymph nodes, and the regional lymph nodes with a 1.5 to 2-cm margin. The fraction size was 1.5 Gy. Regional nodes excluding the contralateral hilar and supraclavicular nodes were included in these fractions. However, lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The second fraction of each day consisted of bilateral oblique fields that encompassed the primary tumor and the metastatic lymph nodes with a 1.5 to 2-cm margin; the fraction size was 1.8 Gy. Attempts were made to design the field of the second fraction to minimize the irradiated volume of the esophagus without compromising the margin around the tumor or spinal cord.

Toxicity assessment

Patients were observed weekly during treatment to monitor toxicity. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Late toxicity was graded according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Late toxicity was defined as that occurring more than 90 days after treatment initiation.

Follow-up evaluation

The following evaluations were performed until disease progression every 2 months for the first year, every 3 months for the second year, and every 6 months thereafter: physical examination, toxicity assessment, and chest radiograph. CT scan of the chest was performed at 1, 3, 6, 9, 12, 18, and 24 months after the treatment and when indicated thereafter. Restaging at 6 months after the treatment was also performed with ultrasound of the abdomen, MRI or CT scan of the brain, and bone scintigraphy.

Response assessment

Complete response (CR) was defined as complete disappearance of all measurable and assessable lesions for ≥ 4 weeks, partial

response (PR) was defined as a decrease of 50% or more from baseline in the sum of products of perpendicular diameters of all measurable lesions for ≥ 4 weeks, and progressive disease (PD) was defined as an increase of 25% or more from baseline in the sum of products of perpendicular diameters of all measurable lesions or the appearance of any new lesion. Stable disease was defined as the remainder of evaluable patients without CR, PR, or PD.

Pattern of failure

Patterns of failure were defined as first site of failure. Local/regional failure included the primary tumor and regional lymph nodes. Distant failure included any site beyond the primary tumor and regional lymph nodes.

Statistics

A Simon's two-stage optimal design was used for this study with the assumption that a protocol compliance rate of less than 60% would not be feasible, and protocol compliance rate of 80% or greater with α error of 0.10 and β error of 0.10 would warrant further investigation of this regimen. In the first stage, 11 assessable patients were entered. If fewer than 7 patients completed the treatment, accrual would be stopped with the conclusion that the regimen was not feasible for further investigation. If 7 or more patients completed the treatment, an additional 27 patients would be accrued in the second study. According to this design, this study would be determined to be feasible and be proceeded to a multicenter Phase II study if 27 patients completed the treatment. The actuarial median survival time and 2-year survival were estimated by the Kaplan-Meier method (11).

RESULTS

Patient population

Between July 1999 and March 2001, 30 patients were enrolled in the study. The accrual was stopped, because 29 of 30 patients completed the treatment, and conclusions could be drawn at that time. The patients' median age was 64 years (range, 46–73 years), 24 were male, and 6 were female. The patient and tumor characteristics are summarized in Table 1.

Treatment compliance and toxicity

All patients completed 2 cycles of induction chemotherapy. Six of 30 patients required dose modification, and 13 patients had treatment delay. The median time to start of HART from start of chemotherapy was 49 days (range, 41–62 days). Twenty-nine of 30 patients completed HART, and the median overall treatment time of HART was 17 days (range, 16–22 days). In total, 29 of 30 patients (97%; 95% confidence interval [CI], 83–100%) completed this combined treatment.

The toxicity profile of the treatment is shown in Tables 2 and 3. Common Grade 3 or greater acute toxicities were neutropenia, 25 (83%); infection, 5 (17%); esophagitis, 5 (17%); and radiation pneumonitis, 3 (19%). There were 2 cases of treatment-related death due to radiation pneumonitis. As of the date of this analysis, 2 cases with Grade

Table 1. Patient and tumor characteristics

Number of patients	30
Age	
Median	64
Range	46-73
Gender	
Male	24
Female	6
Performance status	
0	8
1	22
Weight loss	
<5%	25
≥5%	5
Tumor and lymph nodes	
T1N2	3
T1N3	1
T2N2	5
T2N3	5
T3N2	1
T4N0	1
T4N1	4
T4N2	9
T4N3	1
Stage	
IIIA	9
IIIB	21
Histology	
Squamous	13
Nonsquamous	17

3 s.c. tissue fibrosis and 1 case with spontaneous rib fracture were observed as late toxicities.

Response and survival

Of 30 patients, 2 achieved CR, and 23 achieved PR with a response rate of 83% (95% CI, 65-94%). Five patients remained in a stable disease state, and there were no PD patients. With a median follow-up period of 40 months for surviving patients, the median survival and the 2-year and 3-year survivals (Fig. 1) were 24 months (95% CI, 13-34 months), 50% (95% CI, 32-68%), and 32% (95% CI, 15-49%), respectively. The median progression-free survival and the 1-year progression-free survival (Fig. 2) were 10 months (95% CI, 8-20 months) and 47% (95% CI, 29-65%), respectively.

Pattern of failure

At the time of this analysis, 22 of 30 patients (73%) showed tumor progression, 2 patients (7%) had died as a result of treatment, and 6 patients (20%) were alive without disease progression. The patterns of first failure were as follows: local/regional only, 13 (43%); local/regional and distant, 4 (13%); distant only, 5 (17%).

DISCUSSION

In the 1970s, treatment of locally advanced NSCLC was by conventional radiotherapy alone. In the 1980s, sequential chemotherapy and conventional radiotherapy

Table 2. Hematologic toxicities (n = 30)*

	Grade					≥Grade 3 (%)
	0	1	2	3	4	
Leukopenia	1	3	8	16	2	18 (60)
Neutropenia	3	0	2	6	19	25 (83)
Thrombocytopenia	20	7	1	2	0	2 (7)
Anemia	1	10	16	3	0	3 (10)

* National Cancer Institute-Common Toxicity Criteria version 2.

were revealed to be superior to conventional radiotherapy alone. In the 1990s, optimal sequences of chemoradiotherapy and radiation fractionation were investigated. The West Japan Lung Cancer Group compared sequential vs. concurrent radiotherapy with induction CDDP, vindesine, and mitomycin (7). In an RTOG 9410 trial, induction CDDP and vinblastine plus sequential standard radiotherapy, CDDP and vinblastine plus concurrent standard radiotherapy, and CDDP and etoposide plus concurrent twice-daily hyperfractionated radiotherapy were compared (8). Both trials showed similar results; concurrent chemoradiotherapy was superior to the sequential approach and achieved 5-year survivals for concurrent and sequential approach of approximately 20% and 10%, respectively. However, twice-daily hyperfractionated radiotherapy, which seemed to be promising in a preceding RTOG 9015 trial (12), failed to show a survival advantage over standard once-daily radiotherapy, and concurrent chemotherapy and once-daily radiotherapy is the standard of care today. Recently, a Czech randomized Phase II trial (13) suggested a similar advantage of the concurrent approach using CDDP and VNR, a newer cytotoxic agent. However, there remains some argument that newer cytotoxic agents cannot be delivered as full-dose chemotherapy with concurrent radiotherapy, and the survival advantage of newer cytotoxic agents over old ones has not yet been demonstrated in Stage III NSCLC patients. The optimal schedule and fractionation of thoracic radiotherapy in combination with chemotherapy also remains to be determined.

Another promising regimen was altered fractionation of radiotherapy such as CHART or HART, 3 times a day with a fraction interval of 4 to 6 hours over 2.5 weeks or less. CHART was developed at Mount Vernon Hospital, United Kingdom, in the 1980s. It was designed to combine both a shortening of the overall treatment time of radiotherapy, which is analogous to the concept of dose intensification of cytotoxic chemotherapy, and a reduction in dose per fraction. The rationale was to overcome accelerated repopulation of the tumor during the course of radiotherapy, which may lead to local failure, and to reduce normal tissue toxicities that depend on the dose per fraction. After the results of a randomized trial that showed survival benefits of CHART over conventional

Table 3. Nonhematologic toxicities (n = 30)*

	Grade						≥Grade 3 (%)
	0	1	2	3	4	5	
Acute toxicity							
Nausea	7	16	4	3	0	0	3 (10)
Vomiting	23	3	4	0	0	0	0
Infection	20	3	2	5	0	0	5 (17)
Esophagitis	1	11	13	4	1	0	5 (17)
Pneumonitis	18	4	5	1	0	2	3 (10)
Late radiation morbidity†							
Esophagus	26	1	0	0	0	0	0
Heart	26	0	1	0	0	0	0
Lung	9	13	5	0	0	0	0
Subcutaneous tissue	17	6	2	2	0	0	2 (7)
Bone	26	0	0	0	1	0	1 (3)

* National Cancer Institute–Common Toxicity Criteria version 2.

† Three patients died within 90 days of the beginning of radiotherapy.

radiotherapy (9), the Department of Health in the United Kingdom recommended CHART as the radiotherapy schedule of choice in inoperable NSCLC, and a CHART implementation group was formed to facilitate its introduction throughout the United Kingdom (14). There were difficulties in changing departmental working hours and a lack of sufficient financial support in UK hospitals to introduce CHART into routine practice (15), although it was suggested that CHART gave more benefit than any sequential combination of conventional radiotherapy and chemotherapy with minimally increased toxicity. To make the accelerated regimen more widely applicable, Continuous Hyperfractionated Accelerated Radiotherapy Week-End Less (CHARTWEL) and HART were introduced and were found to be as effective as CHART. Both CHARTWEL and HART showed improved survival over conventional radiotherapy, but the local tumor control was still unsatisfactory. Radiation dose escalation and

use of chemotherapy combined with CHARTWEL/HART were also investigated to improve the local control and survival. Saunders *et al.* (16) reported on CHARTWEL combined with induction chemotherapy (17). In that study, 113 patients were enrolled, and dose escalation from 54 Gy to 60 Gy with or without chemotherapy was successfully achieved. Locoregional control at 2 years was 37% and 55% for CHARTWEL 54 Gy and 60 Gy alone, respectively, compared with 72% in those treated with 60 Gy and induction chemotherapy. These results suggested that chemotherapy improved locoregional control, but unfortunately they failed to show a statistically significant survival advantage, because of the relatively small number of patients and imbalanced tumor characteristics enrolled in each arm. The advantage of dose-escalated CHARTWEL against conventional radiotherapy is currently being investigated in a German Phase

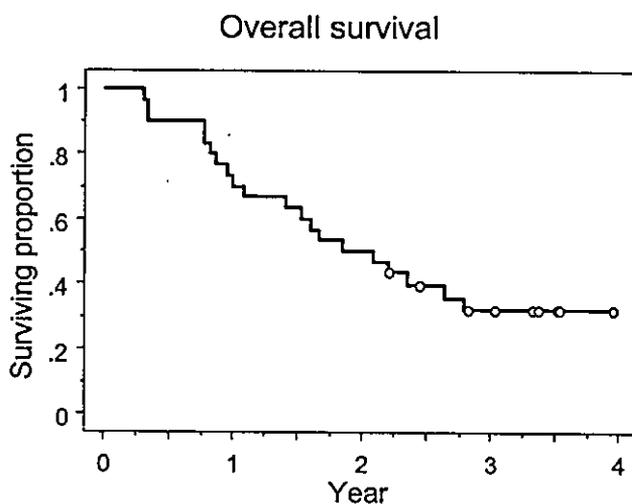


Fig. 1. Overall survival for all patients enrolled in this study.

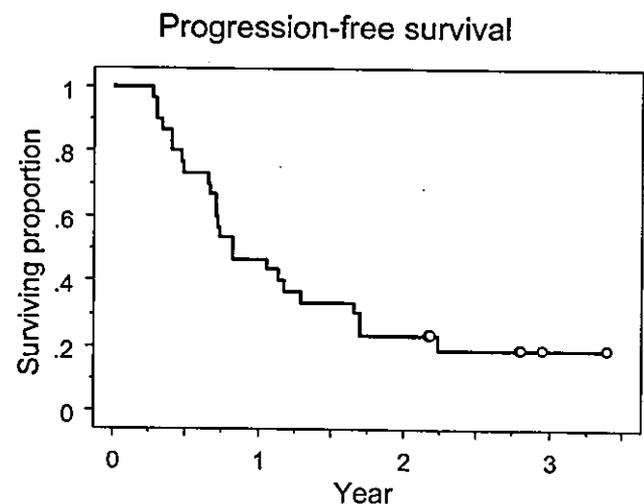


Fig. 2. Progression-free survival for all patients enrolled in this study.

III trial (18). Belani *et al.* reported the results of a randomized Phase III trial (19) that compared conventional radiotherapy with HART after induction chemotherapy (ECOG 2597). This study randomized 119 patients and unfortunately was closed because of slow accrual, but the results were provocative: The median survival time and the 2-year survivals for conventional radiotherapy and HART were 13.7 months and 33% vs. 22.2 months and 48%, respectively. These results seemed to be reliable despite the modest number of patients, because the median survival time of 13.7 months for the conventional radiotherapy arm was similar to that of a sequential chemoradiotherapy trial (2). The optimum chemotherapy regimen in combination with radiotherapy has not yet been determined, and we used a CDDP/VNR regimen instead of the carboplatin/paclitaxel regimen used in the ECOG 2597 trial. Both regimens are standards for advanced-stage NSCLC (20, 21). The compliance and toxicity profiles of chemotherapy in our study were acceptable, the incidence of esophagitis after HART was less than we expected, and the survival figure was nearly identical to that of the ECOG 2597 trial. This suggests that HART after induction CDDP/VNR or carboplatin/paclitaxel can achieve reproducible and promising results.

The pattern of failure in our study showed that local

failure was still high (17 of 30, 57%) compared with distant metastasis (9 of 30, 30%), and further improvement of local control is needed. Future directions may include further dose intensification of radiotherapy and introduction of molecular-targeted agents. Recent innovation of information technology has made it possible to use sophisticated three-dimensional conformal radiotherapy (3DCRT). This can deliver intensified radiation doses to the tumor while minimizing the doses to the normal tissues that prevented further dose escalation using conventional two-dimensional radiotherapy. There have been several reports evaluating dose-intensified 3DCRT (22–25), and the technique is now under investigation in combination with cytotoxic chemotherapy in the Radiation Therapy Oncology Group trial (RTOG L-0117). Currently, molecular-targeted agents are being investigated most enthusiastically in Phase II and Phase III trials (26–29). It will be determined in the near future whether or not the combination of these agents has a survival impact. However, the optimal combination of these agents, newer cytotoxic agents, radiation fractionation, and 3DCRT will still need to be determined. Further investigation employing dose-intensified radiotherapy will be necessary to make a great leap in the treatment of locally advanced NSCLC.

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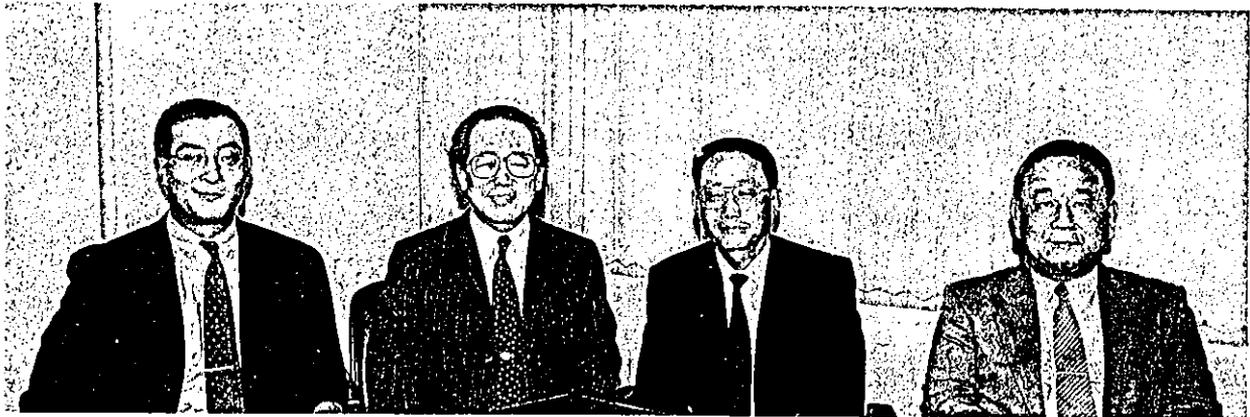
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レスピレーション リサーチ ファンデーション

座談会

肺癌治療における gefitinib (イレッサ®) の臨床的有用性と問題点



貫和 敏博¹⁾(司会)

大江裕一郎²⁾

工藤 翔二³⁾

曾根 三郎⁴⁾

討論内容

イレッサ®の基礎的背景
 イレッサ®使用の臨床現場
 イレッサ®の投与と中止の時期: SDをどう考えるか
 イレッサ®と combination 化学療法 of 臨床試験
 イレッサ®と adverse effect: 薬剤性肺傷害
 日本に薬剤性肺傷害が多いのは事実か?
 Microarray を用いた薬剤効果の評価と個別化医療

Round table talk : Gefitinib (Iressa®) for lung cancer : clinical effectiveness and questions to be answered

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貫和 本日は「肺癌治療における gefitinib (イレッサ®) の臨床的有用性と問題点」ということで座談会をお願いしたいと思います。

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