

These discrepancies may be due to differences in the ethnic background of the populations, the drugs, the study design, and, most important, the accuracy of the molecular analyses. To avoid fruitless controversy, standard methods for analyzing EGFR mutations and copy number should be established.

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TO THE EDITOR: Tsao and colleagues suggest that EGFR mutations were not valuable in predicting a benefit of erlotinib in the BR.21 trial. We believe that the mutation data in their report are inconclusive, for several reasons.

First, in Europe and North America,^{1,2} the frequency of mutations is approximately 10 percent; Tsao et al. report mutations in more than 20 percent of the tumors. Second, only 47 percent of the mutations reported were drug-sensitive exon 19 deletions and L858R substitutions; these make up approximately 90 percent of the EGFR mutations in aggregate in the published data.³ Third, the remaining cases showed “novel variant” mutations whose somatic nature was not established and that were not adequately confirmed. Fourth, these novel mutations were predominantly nucleotide transitions (92 percent), suggesting they were artifacts generated in the polymerase chain reaction (PCR).⁴

Finally, of the 427 patients treated with erlotinib, only 19 who had EGFR mutations could be evaluated. Among these 19 patients, only 8 had tumors with the well-established, drug-sensitive EGFR mutations. At our institution, 33 patients who had tumors containing one of these two common mutations have received erlotinib or gefitinib, and of these, 32 patients (97 percent) have had a response according to the Response Evaluation Criteria in

Solid Tumors; the aggregate published response rate for both drugs and mutations is nearly 80 percent.

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DRS. SHEPHERD AND SEYMOUR REPLY: Patients entering the BR.21 trial after first-line chemotherapy were considered by their doctors not to be suitable candidates for second-line chemotherapy. Physicians had to attest to this, and reasons were recorded and monitored. Thus, these patients could not be compared with patients who participated in the trials cited by Drs. Nabhan and Bitran. We think, therefore, as did ethics review boards and regulatory authorities, that the inclusion of a placebo-control group was ethical, since further chemotherapy was not an option and alternative systemic treatments were unavailable.

It is inappropriate to compare the results of the BR.21, TAX 317,¹ and JMEI² trials, since their patient populations differed considerably. One third of the patients in the BR.21 study had a performance status of between 2 and 3 or 3, as compared with 25 percent of those in the TAX 317 trial and 12 percent of those in the JMEI study. Survival shortens with each successive chemotherapy regimen. In JMEI and TAX 317, 100 percent and 75 percent of patients, respectively, had undergone only one regimen, as compared with 50 percent of the patients in the BR.21 trial. These imbalances in prognostic factors alone could result in shorter survival, independent of treatment.

With regard to patients who were not eligible

for second-line chemotherapy, we think that EGFR inhibitor therapy is ethical on the basis of the BR.21 trial. Whether it should be considered electively for patients who are otherwise suitable candidates for chemotherapy awaits the results of an ongoing study comparing docetaxel with gefitinib.

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DR. TSAO AND COLLEAGUES REPLY: Of 177 tumor samples analyzed in the BR.21 trial, 21 samples (from 20 patients) were exon 19 deletions or L858R substitutions. This rate per patient of 11 percent for classic mutations is similar to that in other reports involving non-Asian patients.^{1,2} The response rate among patients who could be evaluated who had classic mutations was 25 percent (two of eight). Although the rate is lower than that among Asian patients, it probably falls within the confidence interval of other series involving non-Asian patients who did not have adenocarcinoma.

The patients in the BR.21 trial who had classic mutations did not derive a greater survival benefit from erlotinib (hazard ratio for death, 0.67) than those with novel mutations (hazard ratio, 0.65) or those with wild-type EGFR (hazard ratio, 0.73). In the Tarceva Responses in Conjunction with Taxol and Carboplatin (TRIBUTE) trial,³ 29 of 274 (11 percent) of the samples contained mutations (86 percent were classic mutations). Patients who had mutations had longer progression-free survival ($P < 0.001$) and overall survival ($P < 0.001$) than those who did not have mutations, regardless of the type of treatment (chemotherapy with or without erlotinib); the benefit of erlotinib was statistically non-significant. Among patients in the placebo group, those with classic mutations had a longer median survival than those with wild-type or novel EGFR

variants (9.1, 3.5, and 3.5 months, respectively). This suggests that classic EGFR mutations have a prognostic influence that is independent of treatment and that the superior survival reported for mutation-positive patients in uncontrolled studies may not have been due to heightened sensitivity to the EGFR inhibitor.

Dr. Pao and colleagues suggested that novel variants are PCR artifacts caused by formalin fixation. The probability of the appearance of PCR artifacts correlates inversely with the number of cells used for the PCR.¹ However, we found novel mutations more frequently in large biopsy or resection specimens (61 percent) than in small biopsy specimens (41 percent). Chou et al.⁴ also identified several new mutations (V689M, N700D, S720P, V765A, T783A, and G863D) in formalin-fixed tumors from patients who had a response, and the one patient in our series who had a complete response had a transition mutation (V742A[T→C]).

The role of mutations in patients with lung cancer receiving EGFR inhibitors is still evolving. We elected to publish all our mutation results and encourage others to do so as well. Only in this way will sufficient numbers accrue for all mutations to permit clinical correlation. We agree with Takano and Ohe that standard methods for EGFR-mutation analysis and copy number should be established. It is premature to say that EGFR-inhibitor therapy should not be prescribed for patients who do not have EGFR mutations.

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Expert Opinion

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Monthly Focus: Oncologic

Chemoradiotherapy for lung cancer

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Chemoradiotherapy is a standard treatment for both unresectable locally advanced non-small cell lung cancer and limited-stage small cell lung cancer. Cisplatin-based chemotherapy with concurrent thoracic radiotherapy yields a 5-year survival rate of ~ 15% for patients with unresectable locally advanced non-small cell lung cancer. The state-of-the-art treatment for limited-stage small cell lung cancer is four cycles of chemotherapy with cisplatin plus etoposide combined with early concurrent twice-daily thoracic irradiation and prophylactic cranial irradiation after complete remission. A 5-year survival rate of ~ 25% is expected among patients treated for limited-stage small cell lung cancer. The incorporation of new agents, including target-based drugs, is one of the most promising strategies for improving the survival of patients.

Keywords: chemoradiotherapy, fractionation, non-small cell lung cancer, small cell lung cancer, target-based drug

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1. Introduction

Lung cancer has been the most common cancer worldwide since 1985; as of 2002, 1.35 million new cases have been reported, representing 12.4% of all new cancers. It was also the most common cause of death from cancer with 1.18 million deaths: 17.6% of the world total [1]. Lung cancer remains a highly lethal disease. Survival at 5 years measured by the Surveillance Epidemiology and End Results (SEER) programme in the US was 15%: the best recorded rate at the population level. Average survival in Europe is 10%, which is not much better than the 8.9% observed in developing countries [1]. Lung cancer in both men and women continues to be the most common fatal cancer in the US. In 2005 lung cancer is expected to account for 31 and 27% of all deaths from cancer in men and women, respectively, in the US [2]. Nearly 60,000 patients died of lung cancer in 2004, and mortality continues to rise in Japan. In particular, the number of elderly lung cancer patients in Japan is increasing. Lung cancer is the leading cause of cancer death in men and is anticipated to become the leading cause of cancer deaths in women in Japan.

Of lung cancer patients ~ 15 – 20% have small cell lung cancer (SCLC); the remaining patients typically have non-small cell lung cancer (NSCLC), such as adenocarcinoma, squamous cell carcinoma or large cell carcinoma. Surgery is the most effective curative treatment for early-stage NSCLC; however, only 30% of patients with NSCLC receive a curative resection [3]. Platinum-based chemotherapy offers a survival benefit and symptom relief for patients with metastatic NSCLC, and the combination of cisplatin-containing chemotherapy with thoracic radiotherapy is presently the standard treatment for patients with unresectable locally advanced NSCLC [4]. Of patients with unresectable locally advanced NSCLC ~ 15% could be cured by concurrent chemoradiotherapy [5]. Most patients with SCLC are not considered to be candidates for surgery. Combination chemotherapy consisting of cisplatin plus etoposide and concurrent twice-daily thoracic radiotherapy has yielded a 5-year survival rate of ~ 25% in limited-stage (LD) patients [6-8]. Chemoradiotherapy plays a very important

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Table 1. Survival after concurrent chemoradiotherapy for unresectable locally advanced NSCLC and resectable pN2 NSCLC after surgery.

Study	JCOG 9202 [11]	JCOG 9209 [12]
Objective	Unresectable	Resectable, pN2
Treatment	Cisplatin + vindesine + mitomycin Concurrent RT	Surgery with/ without induction cisplatin + vindesine
No. of patients	160	62
No. of institutions	27	18
c-stage		
IIIA/IIIB (%)	29/71	98/2
N0-1/N2/N3 (%)	12/54/34	0/98/2
Survival rate		
2 year (%)	35	36
3 year (%)	22	25
5 year (%)	16	17

JCOG: Japan Clinical Oncology Group; NSCLC: Non-small cell lung cancer.

role in the treatment of both patients with unresectable locally advanced NSCLC and patients with LD-SCLC.

2. Chemoradiotherapy for non-small cell lung cancer

2.1 Patient selection

Patients with stage IIIA or IIIB NSCLC without pleural effusion, pericardiac effusion and/or pleural dissemination are candidates for chemoradiotherapy. Only selected patients with stage IIIA NSCLC are candidates for surgery [9]. Surgery after induction chemotherapy for cytologically proven N2 NSCLC did not improve either overall survival or progression-free survival compared with thoracic radiotherapy [10]. Chemoradiotherapy for unresectable locally advanced NSCLC has achieved a long-term survival rate comparable to that of resectable N2 NSCLC after surgery (Table 1) [11,12]. Patients receiving chemoradiotherapy should have a good performance status and adequate organ function. Only few data exist about the feasibility of chemoradiotherapy in patients with poor performance status. If a patient receives radiotherapy with a radiation field including the contralateral hilum and > 50% of the lung, the patient should be excluded from radiotherapy. Pre-existing pulmonary fibrosis as identified on plain chest X-ray films is a very strong risk factor for treatment-related death after thoracic radiotherapy because of pneumonitis [13,14]. Thus, patients with pulmonary fibrosis identified on plain chest X-ray films should be excluded from radiotherapy.

2.2 Chemoradiotherapy versus radiotherapy alone or chemotherapy alone

A meta-analysis of 1780 cases in 11 randomised trials showed that cisplatin-containing chemoradiotherapy was significantly

superior to radiotherapy alone in terms of survival [4]. Other meta-analyses have also demonstrated the survival superiority of chemoradiotherapy compared with radiotherapy alone, for patients with unresectable locally advanced NSCLC [15,16]. On the other hand, Kubota *et al.* reported that the addition of radiotherapy to chemotherapy for locally advanced NSCLC significantly improved the 2- and 3-year survival rates compared with chemotherapy alone [17]. Sculier *et al.* reported the results of a randomised Phase III trial that compared further chemotherapy and chest irradiation as a consolidation treatment after the achievement of a response to induction chemotherapy in patients with non-metastatic unresectable NSCLC [18]. No significant difference in survival or response duration was seen, but chest irradiation was associated with a significantly greater duration of local control than chemotherapy. Thus, the combination of cisplatin-containing chemotherapy with thoracic radiotherapy has been considered the standard treatment for patients with unresectable locally advanced NSCLC.

2.3 Timing of chemotherapy and radiotherapy

Randomised Phase III trials to compare the sequence schedule of chemoradiotherapy with concurrent chemoradiotherapy have been conducted by the Japan Clinical Oncology Group (JCOG) and by the Radiation Therapy Oncology Group (RTOG) (Table 2) [11,19]. In the JCOG trial, 320 patients with unresectable locally advanced NSCLC were randomised and received chemotherapy with cisplatin, vindesine and mitomycin followed by radiotherapy (sequential arm) or concurrent chemoradiotherapy (concurrent arm). The response rate for the concurrent arm was significantly higher (84%) than that of the sequential arm (66%) ($p = 0.0002$). The median survival duration was significantly longer in patients receiving concurrent therapy (16.5 months) compared with those receiving sequential therapy (13.3 months; $p = 0.03998$). The 2-, 3-, 4- and 5-year survival rates in the concurrent group (34.6, 22.3, 16.9 and 15.8%, respectively) were better than those in the sequential group (27.4, 14.7, 10.1 and 8.9%, respectively). The concurrent approach yielded a significantly higher response rate and enhanced survival duration compared with the sequential approach [11]. Similar results were reported by the RTOG trial. Survival was significantly superior in the concurrent arm, with a median survival time (MST) of 17 months and a 4-year survival rate of 21%, than in the sequential arm, with 14.6 months and 12%, respectively ($p = 0.046$). This report also demonstrated a long-term survival benefit of the concurrent delivery of cisplatin-based chemotherapy with thoracic radiotherapy, compared with the sequential delivery of these therapies [19]. In these trials, acute toxicities such as myelosuppression and oesophagitis were greater among patients in the concurrent arm than in the sequential arm. Based on these Phase III trials, concurrent chemoradiotherapy seems to result in a better survival than sequential therapy.

There are some limitations to the generalisation of the results of these trials because old-generation cisplatin-based

Table 2. Randomised trials of sequential versus concurrent chemoradiotherapy.

Author	Treatment	N	MST (months)	2-year survival	4-year survival	p value
Furuse [11]	CDDP + VDS + MMC sequential TRT	158	13.3	27.4	8.9 (5 years)	0.3998
	CDDP + VDS + MMC concurrent TRT	156	16.6	34.6	15.8 (5 years)	
Curran [19]	CDDP + VBL sequential TRT		14.6	32	12	-
	CDDP + VBL concurrent TRT	610 (total)	17.0	35	21	0.046
	CDDP + ETOP concurrent TRT (twice daily)		15.2	34	17	0.296
Fournel [29]	CDDP + VNR sequential TRT	101	14.5	26	14	0.24
	CDDP + ETOP concurrent TRT followed by CDDP + VNR	100	16.3	39	21	
Zatloukal [30]	CDDP + VNR sequential TRT	50	12.9	14.3	9.5 (3 years)	0.023
	CDDP + VNR concurrent TRT	52	16.6	34.2	18.6 (3 years)	

CDDP: Cisplatin; ETOP: Etoposide; MMC: Mitomycin; MST: Mean survival time; TRT: Thoracic radiotherapy; VBL: Vinblastine; VDS: Vindesine; VNR: Vinorelbine.

combination chemotherapies were used in these trials: cisplatin, vindesine plus mitomycin or cisplatin plus vinblastine [11,19]. These old-generation cisplatin-based chemotherapies could be combined with concurrent radiotherapy using a full dose. Several new anticancer agents were developed in the 1990s, such as irinotecan, paclitaxel, docetaxel, gemcitabine and vinorelbine [20-24]. The combination of platinum and these new agents is more effective than the old-generation combination chemotherapy for metastatic NSCLC [23,24]; however, these new agents cannot be combined with concurrent radiotherapy at the full dose [25-28]. A French cooperative group conducted a Phase III trial to compare sequential versus concurrent chemoradiotherapy for unresectable NSCLC [29]. The sequential arm consisted of three cycles of cisplatin plus vinorelbine followed by thoracic radiotherapy. The concurrent arm consisted of two cycles of cisplatin plus etoposide with concurrent thoracic radiotherapy followed by two cycles of cisplatin plus vinorelbine. A total of 205 patients were enrolled in this trial. The MST was 14.5 months for the sequential arm and 16.3 months for the concurrent arm. The 2-year survival rates were 26 and 39%, respectively [29]. Whereas concurrent therapy tended to be more favourable, the difference was not statistically significant ($p = 0.24$). Zatloukal *et al.* reported the results of a randomised study of concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally

advanced NSCLC [30]. The concurrent chemoradiotherapy arm demonstrated significant benefits in terms of response rate, overall survival and time to progression over the sequential chemoradiotherapy arm. However, they used a reduced dose of vinorelbine in both the concurrent and sequential arms. No data from Phase III trials comparing sequential full-dose, new-generation chemotherapy with concurrent reduced-dose, new-generation chemotherapy are available.

2.4 Fractionation

Radical radiotherapy for NSCLC is most commonly given in daily fractions, Monday to Friday, for a total dose of 60 – 70 Gy over 6 – 8 weeks [31,32]. Novel fractionation schedules have been explored, with the aim of improving local tumour control and survival without increasing late morbidity (Table 3). In hyperfractionated radiotherapy, the dose per fraction is reduced and the total dose is increased to give improved tumour control without increased late morbidity. The clinical trials of RTOG used hyperfractionated radiotherapy, 1.2 Gy/fraction b.i.d. for a total of 69.6 Gy [33]. However, this hyperfractionation schedule did not offer significant benefits when compared with conventional radiotherapy plus chemotherapy [34,35]. Schild *et al.* reported the results of a Phase III study that compared split-course accelerated hyperfractionated radiotherapy (AHFRT), at 1.5 Gy/fraction b.i.d. (60 Gy), with standard radiotherapy (STDRT) at 2 Gy/fraction/day (60 Gy) combined with concurrent chemotherapy

Table 3. Once-daily versus multiple-daily radiotherapy for unresectable NSCLC.

Author	Chemotherapy	Radiotherapy	N	MST (months)	2-year survival (%)	5-year survival (%)	p values
Sause [34,35]	None	2 Gy/day; 60 Gy 5 days/week continuous	163	11.4	21	5	-
	CDDP + VBL induction	2 Gy/day; 60 Gy 5 days/week, continuous	164	13.2	32	8	0.04
	None	1.2 Gy b.i.d.; 69.6 Gy 5 days/week continuous (HFRT)	163	12.0	24	6	NR
Schild [36]	CDDP + ETOP concurrent	2 Gy/day; 60 Gy 5 days/week continuous	117	14	37	13	0.4
	CDDP + ETOP concurrent	1.5 Gy b.i.d.; 60 Gy 5 days/week split (AHFRT)	117	15	40	20	
Saunders [37,38]	None	2 Gy/day; 60 Gy 5 days/week continuous	225	NR	20	NR	0.004
	None	1.5 Gy t.i.d., 54 Gy 7 days/week continuous (CHART)	338	NR	29	NR	
Belani [42]	CBDCA + PTX induction	2 Gy/day; 64 Gy 5 days/week continuous	56	14.9	34	NR	0.28
	CBDCA + PTX induction	1.5 – 1.8 – 1.5 Gy/day; 57.6 Gy 5 days/week continuous (HART)	56	20.3	44	NR	

AHFRT: Accelerated hyperfractionated radiotherapy; CBDCA: Carboplatin; CDDP: Cisplatin; CHART: Continuous hyperfractionated accelerated radiotherapy; ETOP: Etoposide; HART: Hyperfractionated accelerated radiation therapy; HFRT: Hyperfractionated radiotherapy; MST: Median survival time; NR: Not reported; NSCLC: Non-small cell lung cancer; PTX: Paclitaxel; VBL: Vinblastine; VNR: Vinorelbine.

[36]. The toxicity, tumour control and survival rates were similar with AHFRT and STDRT. JCOG retrospectively compared STDRT and AHFRT using data from six JCOG clinical trials [5]. AHFRT did not show a clear tendency to improve the survival of the patients with locally advanced NSCLC. Twice-daily fractionations at doses of 1.2 or 1.5 Gy/fraction were not superior, compared with standard once-daily fractionation, in patients with locally advanced NSCLC.

More recently, continuous hyperfractionated accelerated radiotherapy (CHART) and hyperfractionated accelerated radiation therapy (HART) have been investigated [37-43]. CHART consisted of 36 small fractions of 1.5 Gy given three-times daily, yielding 54 Gy administered on only 12 consecutive days, including the weekend. CHART, compared with conventional radiotherapy, provided a significant improvement in the survival of patients with NSCLC [37,38]; however, this result was obtained from randomised Phase III trials of radiotherapy alone. No randomised trials of chemoradiotherapy using CHART have been reported. HART consisted of a total dose of 57.6 Gy in 36 fractions delivered over 15 days using three-times daily fractions with a 4-h interval between fractions and an 8-h interval between on-cord fields [40-43]. Patients were not treated on

weekends. The results of a Phase III study comparing standard thoracic radiotherapy with HART after induction chemotherapy for patients with unresectable NSCLC were reported by the Eastern Cooperative Oncology Group (ECOG) [42]; however, the study was closed prematurely because of poor patient accrual. Nevertheless, induction chemotherapy of carboplatin plus paclitaxel followed by HART resulted in an acceptable toxicity profile and a provocative efficacy, with a median survival of 20.3 months, in contrast to a median survival of 14.9 months in the standard thoracic radiotherapy arm [42]. Ishikura *et al.* reported the results of a pilot study of HART following induction cisplatin and vinorelbine for stage III NSCLC [43]. A total of 30 patients were enrolled in the study. The overall objective response rate was 83%, and the MST was 24 months. The 2- and 3-year survival rates were 50 and 32%, respectively [43]. Further investigations of CHART or HART with chemotherapy are warranted.

2.5 Selection of anticancer agents

In the 1980s to early 1990s, old-generation cisplatin-based chemotherapy, such as cisplatin plus etoposide, cisplatin plus vindesine, cisplatin plus vinblastin or cisplatin, vindesine plus

Table 4. Randomised Phase II study of chemoradiotherapy for unresectable NSCLC (CALGB94 31) [26].

No. of patients	Induction CT	RT (66Gy) + CT	CR (%)	RR (%)	MST (months)	3-year survival (%)
62	Gem 1250 mg/m ² on days 1, 8, 22 and 29; CDDP 80 mg/m ² on days 1 and 22	Gem 600 mg/m ² on days 43, 50, 64 and 71; CDDP 80 mg/m ² on days 43 and 64	13	74	18.3	28
58	PTX 225 mg/m ² on days 1 and 22; CDDP 80 mg/m ² on days 1 and 22	PTX 135 mg/m ² on days 43 and 64; CDDP 80 mg/m ² on days 43 and 64	33	67	14.8	19
55	VNR 25 mg/m ² on days 1, 8, 15, 22 and 29; CDDP 80 mg/m ² on days 1 and 22	VNR 15 mg/m ² on days 43, 50, 64 and 71; CDDP 80 mg/m ² on days 43 and 64	29	73	17.7	23

CDDP: Cisplatin; CR: Complete response; CT: Chemotherapy; Gem: Gemcitabine; MST: Median survival time; PTX: Paclitaxel; RR: Response rate; RT: Radiotherapy; VNR: Vinorelbine.

mitomycin, were commonly used in chemoradiotherapy according to sequential or concurrent schedules for the treatment of locally advanced NSCLC [5,11,19]. In the 1990s, several new anticancer agents were developed, including irinotecan, paclitaxel, docetaxel, gemcitabine and vinorelbine [20-24]. Most of these new agents have different mechanisms of action from those of the old-generation agents. A full dose of the old-generation combination chemotherapy could be combined with concurrent radiotherapy [11,19]. When combining new-generation chemotherapy and thoracic radiotherapy, however, either reduced-dose chemotherapy with concurrent thoracic radiotherapy or full-dose chemotherapy followed by sequential radiotherapy must be used [25-28]. Full-dose, old-generation combination chemotherapy combined with concurrent radiotherapy and reduced-dose, new-generation chemotherapy combined with concurrent thoracic radiotherapy have not yet been compared. Very few reports have compared chemotherapy regimens with concurrent thoracic radiotherapy. To evaluate the use of the new drugs, gemcitabine, paclitaxel and vinorelbine, in combination with cisplatin in patients with unresectable locally advanced NSCLC, the Cancer and Leukaemia Group B (CALGB) conducted a randomised Phase II study of two cycles of induction chemotherapy followed by two additional cycles of the same drugs with concomitant radiotherapy (Table 4) [26]. A total of 175 patients received four cycles of cisplatin 80 mg/m² on days 1, 22, 43 and 64 with gemcitabine 1250 mg/m² on days 1, 8, 22 and 29 and 600 mg/m² on days 43, 50, 64 and 71, or paclitaxel 225 mg/m² for 3 h on days 1 and 22 and 135 mg/m² on days 43 and 64, or vinorelbine at 25 mg/m² on days 1, 8, 15, 22 and 29 and at 15 mg/m² on days 43, 50, 64 and 71. Radiotherapy was initiated on day 43 at 2 Gy/day for a total dose of 66 Gy. The response rates after completion of radiotherapy were 74, 67 and 73% for the gemcitabine, paclitaxel and vinorelbine arms, respectively. The MSTs were 18.3 (95% confidence interval [CI] 13.8 – 23.6), 14.8 (95% CI 12 – 19.5) and 17.7 months (95% CI 12.4 – 24.7) for the gemcitabine, paclitaxel and vinorelbine arms, respectively [26]. No consistent

standard chemotherapy regimens for chemoradiotherapy have been established.

Concomitant low-dose daily or weekly chemotherapies are also used for chemoradiotherapy as a radiosensitiser. Cisplatin or carboplatin have been commonly used in studies to investigate sensitising effects [44-47]. Of the numerous single-platinum studies, only one Phase III study demonstrated a survival benefit for the daily administration of cisplatin with thoracic radiotherapy [44]. Two studies demonstrated prolonged survival with concomitant, platinum-based, multi-drug chemotherapy and hyperfractionated radiotherapy [48,49]. No data from large Phase III studies comparing full-dose chemotherapy with low-dose sensitising chemotherapy combined with concurrent radiotherapy for the treatment of locally advanced NSCLC have been reported. CALGB conducted a Phase III study to compare low-dose weekly carboplatin plus paclitaxel with concomitant radiotherapy (arm 1) and induction chemotherapy with full-dose carboplatin plus paclitaxel followed by the same concomitant chemoradiotherapy (arm 2) for stage III NSCLC [50]. A total of 366 patients were entered in the study. The median survival in arm 1 was 11.4 versus 14.0 months in 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 with other recent trials. This result indicated that low-dose weekly carboplatin plus paclitaxel with concomitant radiotherapy may be insufficient for the treatment of stage III NSCLC. Induction chemotherapy with full-dose carboplatin plus paclitaxel, followed by radiotherapy with concomitant low-dose weekly chemotherapy with carboplatin plus paclitaxel, was not superior in terms of survival compared with the same induction chemotherapy followed by radiotherapy alone [51]. Not only do the systemic effect of low-dose weekly or daily chemotherapy, such as carboplatin plus paclitaxel, remain unclear, but so do the radiosensitising effects.

The Southwest Oncology Group (SWOG) conducted a Phase II study of concurrent chemoradiotherapy with cisplatin

plus etoposide followed by consolidation docetaxel in patients with stage IIIB NSCLC [52]. Treatment consisted of cisplatin 50 mg/m² on days 1, 8, 29 and 36, etoposide 50 mg/m² on days 1–5 and 29–33, and concurrent thoracic radiotherapy, with a total dose of 61 Gy. Consolidation docetaxel was started 4–6 weeks after chemoradiotherapy at an initial dose of 75 mg/m². A total of 83 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 [52]. Recently, long-term follow-up data revealing a 5-year survival rate of 29% was reported [53]. These results are much better than the results of the previous SWOG trial. To evaluate the feasibility and efficacy of docetaxel consolidation therapy following cisplatin, vinorelbine and concurrent thoracic radiotherapy in patients with unresectable stage III NSCLC, the authors conducted a feasibility study [54]. Among 97 patients the response rate was 82%, the median progression-free survival period was 12.8 months, and the MST was 30.8 months. Although this regimen was effective, the docetaxel consolidation compliance was very poor, with only one third of the patients completing all three cycles of consolidation docetaxel [54]. Phase III trials evaluating docetaxel consolidation have been initiated to validate these results.

2.6 Incorporation of target-based drugs

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors such as gefitinib, erlotinib and cetuximab are one of the most promising kinds of target-based agents for NSCLC [55,56]. Strong preclinical evidence indicates that EGFR inhibition is additive or synergistic with radiotherapy in NSCLC [57–61]. A large, randomised, Phase III trial comparing definitive dose radiotherapy with or without cetuximab in locally advanced head and neck cancer has been completed and reported [62]. The addition of cetuximab to radiotherapy improved locoregional control. More importantly, the MST was prolonged from 28 to 54 months, and the 3-year survival rate was increased from 44 to 57% in the treatment arm receiving radiation plus cetuximab [62]. CALGB 30106 and a multi-institutional Australian Phase I trial have shown that gefitinib can be added to concurrent chemoradiotherapy for stage III NSCLC without excessive toxicity [63,64]. A Phase I trial at the University of Chicago evaluated erlotinib with concurrent chemoradiotherapy in patients with stage III NSCLC [65]. Thus, the combination of gefitinib or erlotinib with chemoradiotherapy is a candidate strategy for improving the survival of patients with unresectable locally advanced NSCLC. JCOG has started a safety and efficacy trial of induction chemotherapy with cisplatin and vinorelbine followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced NSCLC (JCOG 0402-MF). SWOG 0023 is a large, Phase III, randomised trial comparing concurrent chemoradiotherapy and consolidation docetaxel with or without maintenance small-molecule therapy with gefitinib [66]. Unfortunately, SWOG 0023 was closed based on the

interim analysis, which showed that the continuation of SWOG 0023 would not have shown a survival benefit for gefitinib. These results may indicate that the maintenance use of gefitinib after induction chemoradiotherapy does not improve the survival of patients with locally advanced NSCLC; however, the incorporation of EGFR tyrosine kinase inhibitors in chemoradiotherapy is still an attractive strategy for locally advanced NSCLC.

The combination of antiangiogenic agents and radiotherapy is also an attractive strategy. *In vivo* and *in vitro* studies supported that the combination of radiation with an antiangiogenic agent, angiostatin, improved tumour eradication without increasing deleterious effects [67]. Recent Phase III studies demonstrated the survival benefits of the anti-vascular endothelial growth factor antibody bevacizumab in addition to chemotherapy for several kinds of cancer including NSCLC [68]. Thus, a combination of chemoradiotherapy with bevacizumab is also a candidate strategy for improving the survival of patients with unresectable locally advanced NSCLC. Thalidomide is also well known as an antiangiogenic agent. ECOG is conducting a Phase III study of carboplatin, paclitaxel and radiotherapy with or without thalidomide in treating patients with stage III NSCLC (ECOG 3598) based on their pilot study [69].

COX-2 overexpression in lung cancer is a poor prognostic factor and COX-2 inhibitors add to the efficacy of both chemotherapy and radiotherapy. A pilot study has shown the feasibility of celecoxib with docetaxel plus radiation, and consolidation docetaxel plus cisplatin in inoperable stage IIIa and IIIb NSCLC [70]. Celecoxib (400 mg b.i.d.) administration continued as a maintenance therapy over 6 months for patients.

3. Chemoradiotherapy for small cell lung cancer

3.1 Patient selection

SCLC is generally classified into a two-stage system, LD and extensive disease (ED) [71,72]. In the consensus reports of the International Association of Lung Cancer, LD is defined as disease involvement of one haemithorax including ipsilateral pleural effusion and regional lymph nodes including ipsilateral hilar, bilateral mediastinal and bilateral supraclavicular [71,72]. 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 > 50% of the lung, or those with pre-existent pulmonary fibrosis identified on plain chest X-ray films, should be excluded from chemoradiotherapy [6,13,14].

3.2 Standard chemoradiotherapy for small cell lung cancer

A meta-analysis including 13 trials and 2140 patients with LD-SCLC demonstrated a survival benefit of chemoradiotherapy, compared with chemotherapy alone [73]. The relative risk of

Table 5. Twice- versus once-daily radiotherapy for limited-stage small cell lung cancer.

Author	Chemotherapy	Radiotherapy	N	MST (months)	5-year survival (%)	p values
Turrisi [8]	CDDP + ETOP x four cycles	1.5 Gy b.i.d.; 45 Gy, 1st cycle continuous	211	23	26	0.04
	CDDP + ETOP x four cycles	1.8 Gy/day; 45 Gy, 1st – 2nd cycle continuous	206	19	16	
Bonner [75] Schild [76]	CDDP + ETOP x six cycles	1.5 Gy b.i.d.; 48 Gy, 4th – 5th cycles split	130	20.6	22	0.68
	CDDP + ETOP x six cycles	1.8 Gy/day; 50.4 Gy, 4th – 5th cycles continuous	132	20.6	21	

CDDP: Cisplatin; ETOP: Etoposide; MST: Median survival time.

death in the chemoradiotherapy group, compared with the chemotherapy group, was 0.86 (95% CI 0.78 – 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 presently regarded as 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. Recently, cisplatin plus etoposide has become widely regarded as a standard chemotherapy for LD-SCLC, particularly because this regimen can be integrated with concurrent thoracic irradiation with acceptable toxicity [74]. Early thoracic irradiation with concurrent cisplatin plus etoposide chemotherapy is the state-of-the-art treatment for LD-SCLC.

A US intergroup trial demonstrated a survival benefit of twice-daily accelerated thoracic radiotherapy over once-daily radiotherapy with cisplatin plus etoposide for LD-SCLC (Table 5) [8]. A total of 417 LD-SCLC patients were randomised 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- and 5-year survival rates were 41 and 16%, respectively, for patients receiving once-daily radiotherapy, and 47 and 26%, respectively, for the twice-daily group ($p = 0.04$ by the log-rank test) [8]. In contrast, another Phase III trial using split-course twice-daily radiotherapy failed to demonstrate a survival benefit of twice-daily radiotherapy with cisplatin plus etoposide [75,76]. A split radiotherapy schedule seems to diminish the benefit of twice-daily radiotherapy (Table 4).

The brain is one of the most common relapse sites of SCLC. However, the CNS is protected 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 [77-79]. A meta-analysis using individual data for 987 patients with SCLC in complete remission (CR) who took part in seven trials comparing PCI with no PCI demonstrated a survival benefit [80]. The relative risk of death³ in the PCI group, compared with the no PCI group, was 0.84 (95% CI 0.73 – 0.97; $p = 0.01$)⁴, corresponding to a 5.4% increase in the rate of survival at 3 years (15.3% in no PCI group versus 20.7% in PCI group). This absolute improvement in 3-year survival (5.4%) was the same as that shown in the meta-analysis comparing chemotherapy with chemoradiotherapy for SCLC [73,80]. Thus, PCI for SCLC, in patients who achieved a CR, has similar power to improve survival as that of thoracic radiotherapy for LD-SCLC.

The state-of-the-art treatment for LD-SCLC is 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 ~ 25% is expected using this state-of-the-art treatment for LD-SCLC.

3.3 Incorporation of new drugs

JCOG conducted a randomised, multi-centre Phase III study of irinotecan plus cisplatin versus etoposide plus cisplatin for previously untreated ED-SCLC (JCOG 9511) [81]. A total of 154 patients were randomised, 77 into each arm. The MST 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 a significantly better survival, compared with the 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 yielded a highly significant improvement in survival, with less myelosuppression in ED-SCLC patients, over the standard etoposide plus cisplatin treatment [81]. Thus, the incorporation of irinotecan into the treatment of LD-SCLC is considered to be one of the most important strategies for improving the survival of LD-SCLC patients. Concurrent twice-daily thoracic

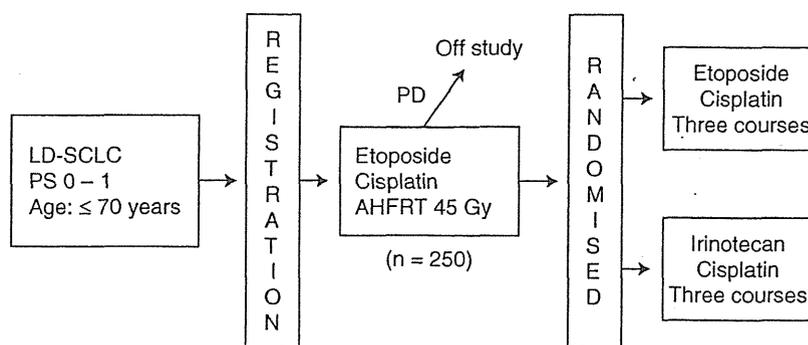


Figure 1. On-going randomised Phase III trial for LD-SCLC in JCOG (JCOG 0202-MF).

AHFRT: Accelerated hyperfractionated radiotherapy; JCOG: Japan Clinical Oncology Group; LD-SCLC: Limited-stage small cell lung cancer; PD: Progressive disease; PS: Performance status.

radiotherapy with combination chemotherapy consisting of irinotecan and cisplatin may be the most powerful treatment for LD-SCLC patients, if the full dose of irinotecan can be used with acceptable toxicity. Previously, JCOG conducted a dose-finding study of irinotecan and cisplatin plus concurrent radiotherapy for patients with unresectable stage III NSCLC (JCOG 9405) [82]. 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 diarrhoea, 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 JCOG 9405. Full-dose chemotherapy consisting of etoposide and cisplatin can even 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 to 60 mg/m² in a weekly schedule [82]. This dose reduction is likely to reduce the efficacy of irinotecan in the treatment of LD-SCLC patients. JCOG is conducting a Phase III study (JCOG 0202-MF) of concurrent twice-daily thoracic radiotherapy with four cycles of etoposide and cisplatin as a 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 (Figure 1).

Amrubicin (SM-5887) is a totally synthetic anthracycline and a potent topoisomerase II inhibitor. 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 9% complete response rate were reported; moreover, the MST was 11.7 months in the single-agent Phase II study of amrubicin [83]. In a combination Phase I/II study of cisplatin plus amrubicin for untreated ED-SCLC, the MST was 13.6 months and the 1-year survival rate was 56.1% [84]. Amrubicin is one of the most active new agents for SCLC. Further clinical development of amrubicin, including chemotherapy for both LD and ED-SCLC, is warranted.

4. Conclusion

Chemoradiotherapy is considered to be the standard treatment for both unresectable locally advanced NSCLC and LD-SCLC [4,73]. Cisplatin-based chemotherapy with concurrent thoracic radiotherapy yields a 5-year survival rate of ~ 15% for patients with unresectable locally advanced NSCLC [5,11,19]. Cisplatin plus etoposide with concurrent twice-daily thoracic radiotherapy also yields a 5-year survival rate of ~ 25% for patients with LD-SCLC [7,8]. Several new strategies are currently underway in an attempt to improve the survival of these patients. The incorporation of target-based drugs such as gefitinib, erlotinib, cetuximab and bevacizumab is considered to be the most promising strategy for unresectable locally advanced NSCLC. The incorporation of irinotecan is also a promising strategy for improving the survival of patients with LD-SCLC. JCOG is presently conducting clinical trials to develop new treatment strategies for both unresectable locally advanced NSCLC and LD-SCLC.

5. Expert opinion

The state-of-the-art treatment for LD-SCLC is four cycles of chemotherapy with cisplatin plus etoposide combined with early concurrent twice-daily thoracic irradiation and PCI after CR [74]. In contrast, no standard treatments for locally advanced NSCLC have been established. Concurrent chemoradiotherapy may be superior to other sequences of chemotherapy and radiotherapy [11,19]. Full-dose, old-generation chemotherapy; reduced-dose, new-generation chemotherapy; and daily or weekly low-dose chemotherapy may be used for concurrent chemoradiotherapy for the treatment of locally advanced NSCLC. No Phase III studies have directly compared chemotherapy with concurrent radiotherapy. The systemic effect of low-dose weekly or daily chemotherapy and also the radiosensitising effects are still unclear. Recent results of a Phase III study indicate that weekly low-dose chemotherapy with radiotherapy may be

inferior to full-dose, old-generation chemotherapy or reduced-dose, new-generation chemotherapy [50]. The role of consolidation docetaxel is still under evaluation in a Phase III study; however, very promising survival data has

been reported by a recent clinical trial using new-generation chemotherapy [52-54]. A Phase III study to establish a standard chemoradiotherapy for locally advanced NSCLC may be warranted.

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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 \geq 2000/mm³, platelets \geq 100 000/mm³, hemoglobin \geq 10 g/dl]; adequate hepatic function [total bilirubin within 1.5 \times the upper limit of normal; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within 2.5 \times 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 \times the upper limit of normal; total bilirubin >1.5 \times the upper limit of normal; creatinine >1.3 \times 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 \geq 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 \times the upper limit of normal during the previous course.

The dose-limiting toxicity (DLT) was defined as follows: grade 4 leukopenia or neutropenia for \geq 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

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.

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 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
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 ± 0.04	2.29 ± 0.31	46.6 ± 11.0	13.6 ± 1.8	2995 ± 434
	4	3	0.08 ± 0.01	2.89 ± 0.34	50.0 ± 10.6	11.6 ± 1.9	3511 ± 514
45 mg/m ²	3	1	0.13 ± 0.05	2.39 ± 0.34	56.3 ± 10.6	14.9 ± 1.8	3052 ± 402
	3	3	0.09 ± 0.03	2.27 ± 0.18	51.9 ± 3.7	14.2 ± 2.3	3217 ± 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 amrubicinol 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 ± 3.1	1412 ± 314
	4	3	20.7 ± 4.8	2159 ± 622
45 mg/m ²	3	1	19.6 ± 6.1	1098 ± 277
	3	3	18.1 ± 5.7	2027 ± 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

	<i>n</i>	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.

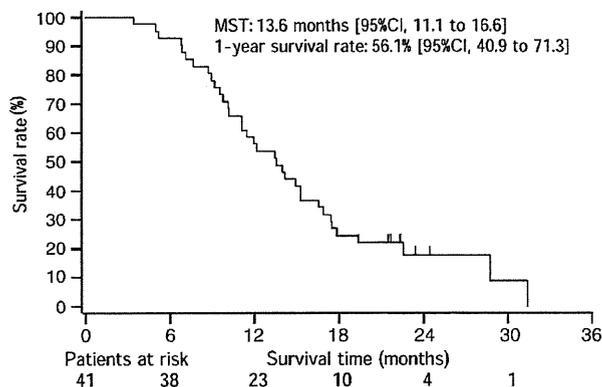


Figure 1. Overall survival of patients with extensive-stage small-cell lung cancer who were treated with amrubicin and cisplatin at the recommended dose. MST, median survival time; 95% CI, 95% confidence interval.

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-naive 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-naive 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-naive 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 overselection 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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