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A Phase II Study of Cisplatin and Irinotecan as Induction Chemotherapy Followed by Accelerated Hyperfractionated Thoracic Radiotherapy with Daily Low-dose Carboplatin in Unresectable Stage III Non-small Cell Lung Cancer: JCOG 9510

Tomoki Fujii[1], Hiroshi Kunikane[1], Hiroaki Okamoto[1], Koshiro Watanabe[1], Hideo Kunitoh[2], Kiyoshi Mori[3], Akira Yokoyama[4], Haruhiko Fukuda[5], Tomohide Tamura[6] and Nagahiro Saijo[7]

[1]Department of Respiratory Medicine and Medical Oncology, Yokohama Municipal Citizen's Hospital, Kanagawa, [2]Department of Respiratory Medicine, Mitsui Memorial Hospital, Tokyo, [3]Department of Internal Medicine, Tochigi Prefectural Cancer Center, Tochigi, [4]Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, [5]Japan Clinical Oncology Group Data Center, Center for Cancer Control and Information Services, National Cancer Center, [6]Department of Thoracic Oncology, National Cancer Center Hospital Central, Tokyo and [7]Department of Medical Oncology, Kinki University School of Medicine, Osaka, Japan

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Objective: It is important to find optimal regimens of cisplatin (CDDP)-based third-generation chemotherapy and radiotherapy for patients with unresectable Stage III non-small cell lung cancer (NSCLC).
Methods: This Phase II study was designed to determine the toxicity and efficacy of two courses of chemotherapy (CDDP 80 mg/m^2 on day 1 and irinotecan 60 mg/m^2 on days 1 and 8) followed by accelerated hyperfractionated thoracic radiotherapy (60 Gy/40 fractions in 4 weeks) combined with daily carboplatin (CBDCA) administration. CBDCA was administered at a target area under the plasma level–time curve of 0.4 × (24 h creatinine clearance + 25), according to Calvert's formula.
Results: Twenty-six patients were enrolled in the study. The patients' median age was 63 years (range 40–74 years) and included 22 males and 4 females. Seven patients were Stage IIIA and 19 were Stage IIIB. Twenty had a performance status (PS) of 1 versus six with a PS of 0. There was one treatment-related death due to sepsis and pneumonia associated with Grade 4 neutropenia and diarrhea during chemotherapy. Grade 3 or 4 neutropenia and diarrhea were observed in 14 and 5 patients, respectively. Toxicity of the radiotherapy was mild. There were 0 complete response and 13 partial responses, giving a response rate of 50.0%. Median survival time and 2-year survival were 16.4 months and 21.5%, respectively. This study was designed with Simon's two-stage design, and the response rate did not meet the criteria to proceed to the second stage and the study was terminated early.
Conclusions: This regimen might be inactive for patients with unresectable Stage III NSCLC.

Key words: cisplatin – irinotecan – carboplatin – chemoradiotherapy – non-small cell lung cancer

INTRODUCTION

Over the past 2 decades, a great number of clinical trials have gradually proven the benefits of a chemotherapeutic approach for treatment of unresectable non-small cell lung cancer (NSCLC) (1,2). In unresectable Stage III NSCLC, in which the tumor is apparently confined to the chest but is surgically unresectable, several randomized trials have shown that combinations of chemotherapy and thoracic radiotherapy have improved survival compared with radiotherapy alone (3–6). It is important to find optimal regimens of combined chemotherapy and radiotherapy and to evaluate the feasibility and efficacy of those combinations.

For reprints and all correspondence: Hiroaki Okamoto, Department of Respiratory Medicine and Medical Oncology, Yokohama Municipal Citizen's Hospital, 56 Okazawa-cho, Yokohama 240-8555, Japan.
E-mail: scyooka@alles.or.jp

Irinotecan (CPT-11) is an antitumor agent which inhibits the nuclear enzyme topoisomerase I (7,8). CPT-11 has played a significant role in the development of chemotherapy for NSCLC since the initial reports of its efficacy as a single agent (9,10). Combination chemotherapy of CPT-11 and cisplatin (CDDP), which is also a commonly used agent for NSCLC, is a promising regimen for NSCLC, as its high antitumor activity and manageable toxicity have been reproducibly reported (11,12). One critical but uncommon toxicity of CPT-11 is reported to be pulmonary toxicity (10), and it is necessary to clarify how the chemotherapy regimen should be combined with thoracic radiotherapy in patients with Stage III NSCLC.

In addition to combined radio-chemotherapy, concomitant treatment with low doses of radiosensitizers has also been investigated in patients with Stage III NSCLC. Schaake-Koning et al. (13) reported that daily low-dose CDDP combined with thoracic radiation improved the local control of tumors in a randomized study. Furthermore, its favorable results were also confirmed in another Phase II study (14). Carboplatin (CBDCA) has also been investigated as a radiosensitizer (15). It has been suggested that CBDCA may be superior to CDDP in this role because it would provide a greater platinum concentration within cells at the time of irradiation (16). We have reported the concurrent daily CBDCA (25 mg/m^2) and accelerated hyperfractionated thoracic radiotherapy (AHRT) in locally advanced NSCLC (17). Of the 31 patients, the response rate was 84% (26/31) and the median survival time (MST) was 9.8 months. Major acute toxicity (Grade $\geq$3) included 55% with leukopenia, 16% with thrombocytopenia and 23% with esophagitis. Area under the plasma level–time curve (AUC) of CBDCA was significantly correlated with efficacy and leukopenia. In this setting, we concluded that daily CBDCA AUC of 0.4 plus concurrent AHRT was the most effective and safe treatment in locally advanced NSCLC.

On the other hand, the CDDP plus CPT-11 regimen is one of the standard platinum-based combination chemotherapies including a new agent in Stage IIIB/IV NSCLC in Japan (11). Therefore, in order to improve therapeutic outcome in patients with unresectable Stage III NSCLC, we have conducted a Phase II study of a regimen of two courses of CDDP plus CPT-11 as an induction chemotherapy, followed by AHRT with daily low-dose CBDCA administration.

PATIENTS AND METHODS

Patient Selection

Patients with histologically or cytologically confirmed unresectable Stage III NSCLC who had not received cancer therapy were enrolled in this study. Staging for entry criteria was performed according to the lung cancer staging system of the International Union against Cancer. Staging procedures included chest X-ray, computed tomography (CT) scan of the chest, CT scan or magnetic resonance imaging of the brain, CT scan or ultrasound of the abdomen and isotope bone scanning. N-status was mainly based on size criteria in chest CT scan. Patients with pleural or pericardial effusion were excluded from the study. Each patient was required to meet the following criteria: Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; $<$75 years of age; predicted area of radiation field is less than half of one lung; adequate hematological, pulmonary, renal and hepatic function, i.e. white blood cell (WBC) count $\geq$4000/μL, hemoglobin level $\geq$10 g/dl, platelet count $\geq$130 000/μL, PaO_2 $\geq$70 torr, blood urea nitrogen and serum creatinine level no higher than the upper limit of normal, creatinine clearance (Ccr) $\geq$60 ml/min, serum total bilirubin level $\leq$1.5 mg/dl and serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) levels less than twice the upper limit of normal.

Patients with uncontrolled heart failure or infection, chronic pulmonary disease which restricts thoracic radiation, prolonged diarrhea, ileus, gastrointestinal bleeding or history of myocardial infarction in the last 3 months were excluded from the study. Female patients in pregnancy or lactation during chemotherapy were also excluded. All patients were required to give their own written informed consent.

Treatment Schedule

After enrollment in the study, the patients received chemotherapy consisting of intravenous infusion of 80 mg/m^2 of CDDP on day 1 and 60 mg/m^2 of CPT-11 on days 1 and 8. The chemotherapy was repeated 3–4 weeks after the start of the first course, as long as the patients had sufficiently recovered from toxicity. The chemotherapy was to be performed for two courses, unless unacceptable toxicity or disease progression occurred.

Four weeks after the start of the second course of chemotherapy, thoracic radiotherapy was started. The initial opposing anterior–posterior treatment fields encompassed the primary tumor, the bilateral mediastinal lymph nodes and the ipsilateral hilar nodes. The supraclavicular nodes were included within the field when there was clinical evidence of their involvement. A 1.5 cm tumor-free margin was required. The fraction size delivered was 1.5 Gy, given twice per day, 5 days per week. Thus, the total radiation dose was 60 Gy in 40 fractions over 4 weeks. The methods for spinal block and boost after the first 30 Gy delivery was left to the discretion of the treating radiation oncologist. On each day of thoracic radiotherapy, the patients also received intravenous CBDCA. CBDCA was dosed to a target AUC of 0.4 $\times$ (24 h Ccr + 25), according to Calvert's formula (18), and was administered intravenously over 15 min immediately before the first radiation of the day. The CBDCA AUC of 0.4 was determined based on our previous study (17).

CPT-11 on day 8 was skipped if the WBC count was $<$3000/μL, platelet count $<$75 000/μL or Grade 2 or higher diarrhea or abdominal pain was seen. During chemotherapy, if the WBC count fell $<$2000/μL or the neutrophil count

dropped $<1000/\mu L$, daily granulocyte colony-stimulating factor (G-CSF) was administered subcutaneously until the WBC count increased to $\geq 10\,000/\mu L$ or was no longer clinically indicated. Radiotherapy and concomitant use of G-CSF was contraindicated. When the second course of CDDP plus CPT-11 was started, each patient was required to meet the following criteria: WBC count $\geq 4000/\mu L$, neutrophil count $\geq 2000/\mu L$, platelet count $\geq 130\,000/\mu L$, serum creatinine level ≤ 1.5 mg/dl, serum GOT and GPT levels Grade 0 or 1, Ccr ≥ 30 ml/min, body temperature $<38.0°C$ and PS 0, 1 or 2. For patients receiving G-CSF, 3 days after discontinuation, patients were required to meet the aforementioned hematological toxicity criteria prior to starting the second course of CDDP plus CPT-11. If the second course was delayed 2 weeks or more due to toxicity, chemotherapy with CDDP plus CPT-11 and low-dose CBDCA was terminated and only radiotherapy was used. According to toxicities in the first course of chemotherapy, the dose of CDDP was reduced by 25% for Grade 4 leukopenia, Grade 4 neutropenia ≥ 7 days, Grade 3 thrombocytopenia, Grade 3 or 4 mucositis or Grade 2 or higher renal toxicity, and by 50% for Grade 4 thrombocytopenia. The dose of CPT-11 was reduced by 25% for Grade 3 or 4 diarrhea and administration of CPT-11 was terminated if Grade 2 or higher pulmonary toxicity was seen.

Criteria for starting AHRT with daily low dosage CBDCA administration were the same as mentioned above for the second course of CDDP plus CPT-11. Six weeks after initiation of the second course of chemotherapy, if the same criteria were not fulfilled, CBDCA administration was terminated. In that case, only radiotherapy was used.

During chemoradiation, if the WBC count fell $<2000/\mu L$, neutrophil count $<1000/\mu L$ or platelet count $<50\,000/\mu L$, daily use of CBDCA was suspended and only radiotherapy was continued. After recovery from neutropenia, administration of CBDCA was restarted. In case of Grade 4 hematological toxicities, chemoradiation was to be terminated. However, if any toxicity improved Grade 2 or lower, only radiotherapy could be used. If the PaO_2 level decreased by 10 torr or more compared with baseline value, chemoradiation was suspended and if it returned to baseline, treatment could be started again carefully. If Grade 3 or 4 radiation-related esophagitis was seen, chemoradiation was suspended but could be started again when this toxicity improved to Grade 2 or lower. If patients had a fever of 38°C or higher, chemoradiation was suspended until they were afebrile. Chemoradiation was also suspended when deterioration of PS to 3 or 4 occurred, and PS 0, 1 or 2 was necessary to restart the protocol treatment.

Treatment Evaluation

Tumor response and toxicity were evaluated according to World Health Organization response criteria (19) and Japan Clinical Oncology Group (JCOG) toxicity criteria (20), respectively. Complete response (CR), partial response (PR) and no change (NC) were reviewed and confirmed by central review with chest radiographs or CTs at the regular disease-group meeting. Complete blood cell count and routine blood chemistry were checked twice a week, and arterial blood gas and chest radiographs were checked at least once a week, until the patient had apparently recovered from all acute toxic effects after the completion of the treatment. In this trial, the methods to follow-up the patient after the protocol treatment were not clearly defined. In addition, not only late toxicities but also recurrence patterns after finishing protocol treatment were not routinely recorded in the case report form (CRF). Therefore, the interval of evaluation for late toxicities was left to the discretion of the treating physician. Consequently, the frequency of visiting the doctors and radiologic examinations was heterogeneous among the patients.

Study Design and Statistical Methods

This trial was designed as a multicenter prospective single-arm Phase II study, and the study protocol was approved by the Clinical Trial Review Committee (protocol review committee) of JCOG (21) and the institutional review board of each participating institution before study activation. After pre-treatment staging and eligibility evaluation, patients were registered at the JCOG Data Center by telephone or fax. The study was performed by the JCOG Lung Cancer Study Group and all study data were managed by the JCOG Data Center.

The primary endpoints of this study were the overall response rate (ORR) and overall survival (OS). The ORR was defined as the proportion of the patients with CR or PR out of all eligible patients. The confidence intervals for the ORR were calculated based on the exact method. The OS was measured from the date of patient registration to the date of death due to any cause. If a patient was alive at the final follow-up survey, OS was censored at the last contact date. The estimates of survival distribution were calculated by the Kaplan–Meier method and confidence intervals were based on Greenwood's formula (22). And 2-year OS was expected to be ~40%. The progression-free survival was not measured in this study.

We set an expected level (P1) of response rate as 80%, threshold level (P0) as 60%, α-error level was 0.05 and β-error level was 0.10. We set the planned total sample size as 45 according to Simon's minimax two-stage design (23). If 15 or fewer patients out of 26 patients showed objective responses at the first stage, the study was to be terminated early. The OS was followed up to 20 months after the last enrollment.

RESULTS

Patient Characteristics

Between February 1996 and January 1999, 26 patients from 5 institutions were enrolled in this study and all received induction chemotherapy. The pace of enrollment was approximately one-fourth of the planned one in the protocol.

For the pre-specified first stage decision, the accrual was temporarily closed and the response rate was assessed. Characteristics of the 26 patients are listed in Table 1. The patients included 22 men and 4 women, with a median age of 63 (range, 40–74) years. The histologic classifications included adenocarcinoma in 14 patients and squamous cell carcinoma in 12. Seven patients were in Stage IIIA and 19 were in Stage IIIB. Six patients had ECOG PS of 0 and 20 had that of 1. All of the 26 patients were eligible and evaluable for both tumor response and toxicity.

Treatment Delivery and Protocol Compliance

Of the 26 patients enrolled in the study, 15 completed both of the scheduled chemotherapy and radiotherapy. Protocol compliance in the 26 patients is summarized in Tables 2 and 3. In six patients, treatment was terminated after the first course of chemotherapy. The reasons for the withdrawal were disease progression in three patients and toxicity in three. In three patients with disease progression after the first course of CDDP plus CPT-11, one patient could receive sequential chemoradiation. In one patient Cre >1.5 mg/dl persisted, whereas in another patient, Grade 4 diarrhea, Grade 2 neutropenia and Grade 2 fever caused deterioration of PS and resulted in termination of induction chemotherapy. That patient died of sepsis and pneumonia from Grade 4 neutropenia and diarrhea which we categorized as treatment-related death. One patient had disease progression after two courses of chemotherapy and could not receive radiotherapy. One patient experienced Grade 4 leukopenia and the dose of CDDP in the second course should have been reduced to 75% of the original dosage. However, this patient received only CPT-11 and CDDP was improperly omitted in the second course, which was judged as a protocol violation. Delay in the start of the second course occurred in three patients. CPT-11 administration on day 8 was skipped in four patients and three patients had dose reduction of CPT-11 in the second course. The reason for dose omission or dose reduction was diarrhea in five patients.

Twenty patients received thoracic radiotherapy according to the protocol but 3 of the 20 patients could not receive the whole 60 Gy of radiation with daily CBDCA because of hypoxemia, emesis or onset of herpes zoster in the radiation field in each patient, respectively. Radiotherapy could not be delivered for six patients. The reason for not receiving radiotherapy was disease progression in four patients and toxicity in two patients including treatment-related death in one patient. Of the 20 patients receiving radiotherapy, actual mean radiation dose and actual mean number of CBDCA infusion was 56.8 Gy and 17.5 times, respectively (Table 3).

Table 1. Patient characteristics

Characteristics		No.	%
Age (years)			
Median	63		
Range	40–74		
Sex			
Male		22	84.6
Female		4	15.4
Histology			
Adenocarcinoma		14	53.8
Squamous cell carcinoma		12	46.2
Others		0	0
Clinical Stage			
Stage IIIA		7	26.9
Stage IIIB		19	73.1
T-stage			
T1		4	15.4
T2		6	23.1
T3		5	19.2
T4		11	42.3
N-stage			
N0		2	7.7
N1		2	7.7
N2		11	42.3
N3		11	42.3
Performance status (ECOG)			
0		6	23.1
1		20	76.9

ECOG, Eastern Cooperative Oncology Group.

Table 2. Dose intensity of chemotherapy phase ($n = 26$)

	Planned DI	Actual DI	%[a]
CDDP	26.7	23	86
CPT-11	40	33.3	83

DI, dose intensity (mg/m^2/week); CDDP, cisplatin; CPT-11, irinotecan.
[a]Percentage of the drug dose actually delivered, vs. the planned dose, is presented.

Table 3. Chemoradiation delivery ($n = 20$)

	Planned delivery	Actual delivery, mean
AHRT	60 Gy	56.8 Gy
CBDCA infusion	20 times	17.5 times

AHRT, accelerated hyperfractionated thoracic radiotherapy; CBDCA, carboplatin.

Toxicity

There was one treatment-related death due to septic shock and pneumonia associated with Grade 4 neutropenia, Grade 4 thrombocytopenia and Grade 4 diarrhea. That patient had CDDP and CPT-11 administration on day 1 and CPT-11 on day 8 in the first course and suffered from serious toxicity. *Pseudomonous aeruginosa* was detected in the microbiological culture test from the stool of the patient. This patient died on day 35 from toxicities mentioned above. Toxicities in the 26 patients are listed in Table 4. Grade 3 or 4 neutropenia occurred in 54% of the patients. Grade 3 or 4 thrombocytopenia occurred in four patients and one patient required platelet transfusion.

The most frequent non-hematological toxicity was diarrhea, and Grade 2 or more occurred in 46% of the patients. Five patients had Grade 2 esophagitis during radiotherapy but it did not cause termination of the therapy. Pulmonary toxicity was not evident during the radiotherapy, as well as CPT-11 including chemotherapy. In one patient, radiotherapy was terminated due to a decrease in arterial oxygen pressure by 17 torr when compared with baseline but that patient also had disease progression during the therapy and it was difficult to evaluate the causal relationship to the protocol treatment. In this trial, late toxicities after finishing protocol treatment were not routinely recorded in CRF.

Table 4. Toxicity in 26 patients (JCOG grade)

	0	1	2	3	4
Leukopenia	4	5	10	7	0
Neutropenia	4	2	6	8	6
Anemia	2	4	13	7	—
Thrombocytopenia	16	5	1	3	1
Bilirubin	22	—	3	1	0
GOT	18	7	1	0	0
GPT	10	11	3	2	0
ALP	19	7	0	0	0
Creatinine	21	4	1	0	0
Arterial oxygen pressure	5	18	3	0	0
Hypo/hypernatremia	9	12	4	1	0
Hypo/hyperkalemia	23	1	1	1	0
Emesis	1	13	11	1	—
Cardiac dysfunction	24	1	0	0	1
Proteinuria	22	4	0	0	0
Hematuria	21	5	0	0	0
Diarrhea	3	11	7	3	2
Esophagitis	8	13	5	0	0
Fever	20	3	3	0	0
Weight loss	8	9	8	1	—

JCOG, Japan Clinical Oncology Group; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; ALP, alkaliphosphatase.

Response and Survival

Objective tumor response is summarized in Table 5. Among the 26 patients, there were 13 PRs and 0 CR, giving a response rate of 50% (95% confidence interval, 30–70%). In 10 patients, a PR was achieved before the start of radiotherapy. Disease progression occurred during chemotherapy in four patients, who had to terminate the protocol treatment. Tumor response could not be evaluated in the patient with treatment-related death. The response rate at the first stage did not meet the criteria to proceed to the second stage and the study was terminated early. Figure 1 shows the OS curve of all patients enrolled in the study. After follow-up for 20 months after the last enrollment, the MST was 16.4 months. The 1- and 2-year survival rates in the 26 patients were 65.4% and 21.5%, respectively.

DISCUSSION

The findings of the present study suggest several important points that should be applied in future studies of Stage III NSCLC, although the response rate of this combination therapy was not as high as expected. First, the protocol regimen may not be sufficiently optimized in order to keep high compliance. The inferior tumor response and the high frequency of disease progression during the induction chemotherapy with CPT-11 and CDDP appeared to be the major reason for the disappointing results, which led to the early termination of the present study. Only 10 out of the 26 patients showed >50% tumor reduction during chemotherapy. It appeared unsatisfactory when one considers

Table 5. Clinical response to the therapy in 26 patients

CR	PR	NC	PD	NE	% of CR + PR (95% confidence interval)
0	13	5	7	1	50.0 (29.9–70.1)

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable.

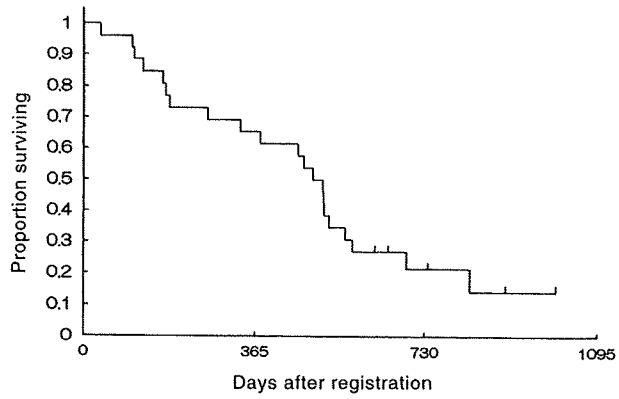

Figure 1. The overall survival curve of all patients enrolled in the study.

that only patients in Stage III were enrolled in the study. Another reason may be the fact that there were comparatively more Stage IIIB patients than Stage IIIA. Although the proportion of Stage IIIA cases was only 26.9% in this trial, in two recent studies, it was 43% and 49% (24,25). This case distribution might have contributed to the poor outcome of this study.

In the view of toxicity management, diarrhea is considered to be key toxicity to be managed carefully in combination chemotherapy using CPT-11. Relative dose intensity of CDDP, CPT-11 and radiotherapy was acceptable in this protocol; however, severe diarrhea caused lowering protocol compliance probably because high-dose loperamide therapy (26) even in the case of severe diarrhea was not used during initial period in this study. It might be possible that the antidiarrhea agent was inadequate and protocol treatment could not be completed in some cases as a result. Had high-dose loperamide therapy been applied appropriately in all eligible cases, better response rate and survival might have been achieved in this study.

It is noteworthy that the strong association between CPT-11 delivery and antitumor response was seen in the present study. In fact, among the 12 patients who had two courses of induction chemotherapy without any delay, omission or dose reduction in CPT-11 administration, 7 showed >50% tumor reduction during the induction chemotherapy and 9 eventually achieved PR after the whole course of therapy (data not shown). This result suggests the possibility that the schedule of CPT-11 administration in this study (days 1 and 8) which was different from the more common regimen (days 1, 8 and 15) may explain the relatively low response rate and the large number of patients with disease progression. Six patients could not receive the protocol radiotherapy because of disease progression or toxicity of the induction chemotherapy. Planned omission of CPT-11 administration on day 15 was intended to reduce risk of pulmonary toxicity during radiotherapy but it might cause unsatisfactory tumor response in the chemotherapy.

Second, the timing of combination of thoracic radiation with chemotherapy may also not be optimized. The present study adopted sequential radiation following induction chemotherapy with CPT-11 and CDDP but suggests that inferior antitumor activity in the chemotherapy could cause failing to receive radiotherapy in some patients. It is difficult to find the best regimen using CPT-11 in the combined modality treatment for Stage III NSCLC.

Because late toxicities were not fully evaluated, the occurrence of both pneumonitis and delayed esophagitis might be possibly underestimated in this study. However, despite the high radiation dose, acute esophagitis were very mild contrary to our expectation, although we cannot clearly explain the reason. Most patients who could proceed to chemoradiotherapy could complete the scheduled radiation with acceptable toxicity. The MST of 16.4 months in the present study was almost as good as in other studies that showed high response rates and survival benefit in Stage III NSCLC. Although our study was prematurely closed after interim analysis because of low response rate, OS which was one of the primary endpoints was comparable with other literatures (24,25,27). In our opinion, AHRT with CBDCA still remains a chemoradiotherapeutic option and should be investigated further with combinations of other chemotherapy regimens.

In recent years, however, some articles have shown that addition of induction chemotherapy before concurrent chemoradiotherapy adds toxicity and provides no survival benefit (24,25). In addition, National Comprehensive Cancer Network (NCCN) practice guideline recommends CDDP plus etoposide or vinblastin with concurrent radiotherapy as preferred standard of cares (category 2A) for patients with unresectable NSCLC (28). Further studies to investigate the role of induction chemotherapy followed by chemoradiotherapy may be not necessary until appearance of more active anticancer agents.

In conclusion, we failed to demonstrate promising efficacy of this regimen, and the development of a brand-new treatment strategy for combining chemotherapy with radiotherapy is necessary for the improvement of the prognosis of the patients with unresectable Stage III NSCLC.

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Conflict of interest statement

None declared.

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Clinical Studies

Randomised phase III trial of carboplatin plus etoposide *vs* split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702

H Okamoto*[,1], K Watanabe[1], H Kunikane[1], A Yokoyama[2], S Kudoh[3], T Asakawa[4], T Shibata[4], H Kunitoh[5], T Tamura[5] and N Saijo[6], on Behalf of the Japan Clinical Oncology Group (JCOG)-Lung Cancer Study Group

[1]Department of Respiratory Medicine, Yokohama Municipal Citizen's Hospital, 56 Okazawa-cho, Hodogaya-ku, Yokohama, Kanagawa 240-8555, Japan; [2]Niigata Cancer Center Hospital, Niigata-city, Japan; [3]Osaka City University Medical School, Osaka-city, Japan; [4]National Cancer Center, Tokyo, Japan; [5]National Cancer Center Hospital, Tokyo, Japan; [6]National Cancer Center East Hospital, Kashiwa, Japan

We compared the efficacy and the safety of a carboplatin plus etoposide regimen (CE) *vs* split doses of cisplatin plus etoposide (SPE) in elderly or poor-risk patients with extensive disease small-cell lung cancer (ED-SCLC). Eligibility criteria included: untreated ED-SCLC; age $\geqslant 70$ and performance status 0–2, or age <70 and PS 3. The CE arm received carboplatin area under the curve of five intravenously (IV) on day 1 and etoposide 80 mg m^{-2} IV on days 1–3. The SPE arm received cisplatin 25 mg m^{-2} IV on days 1–3 and etoposide 80 mg m^{-2} IV on days 1–3. Both regimens were given with granulocyte colony-stimulating factor support in a 21–28 day cycle for four courses. A total of 220 patients were randomised. Median age was 74 years and 74% had a PS of 0 or 1. Major grade 3–4 toxicities were (%CE/%SPE): leucopenia 54/51, neutropenia 95/90, thrombocytopenia 56/16, infection 7/6. There was no significant difference (CE/SPE) in the response rate (73/73%) and overall survival (median 10.6/9.9 mo; $P = 0.54$). Palliation scores were very similar between the arms. Although the SPE regimen is still considered to be the standard treatment in elderly or poor-risk patients with ED-SCLC, the CE regimen can be an alternative for this population considering the risk–benefit balance.
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Approximately half of patients with small-cell lung cancer (SCLC) are older than 70 years, and the proportion of elderly SCLC patients is continuously increasing in Japan (Morita, 2002). However, since many investigators have arbitrarily excluded elderly patients from clinical trials, no standard chemotherapeutic regimen has been established for elderly patients with SCLC. The Japan Clinical Oncology Group (JCOG) has reported that carboplatin plus etoposide (CE) is an active and less toxic regimen in elderly patients with SCLC (Okamoto *et al*, 1999). However, other clinical trials have indicated that the combination chemotherapy of reduced (Souhami *et al*, 1997) or split doses of cisplatin plus etoposide (SPE) (Murray *et al*, 1998; Westeel *et al*, 1998) can be safely and effectively administered in elderly or poor-risk patients with SCLC. Therefore, we conducted a phase III trial comparing CE with SPE in elderly or poor-risk patients with SCLC. Although elderly is not the same as poor-risk, many clinical trials for the elderly have included both types of patients. Therefore, we decided to include both elderly and poor-risk patients with SCLC at the time of proposal for this phase III trial.

*Correspondence: Dr H Okamoto;
E-mail address: scyooka@alles.or.jp
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PATIENTS AND METHODS

Patient selection

Eligibility criteria included patients with histologically or cytologically confirmed SCLC who were $\geqslant 70$ years of age and had an Eastern Cooperative Oncology Group performance status (PS) of 0–2, or who were <70 years in age and had a PS of 3. Additional criteria consisted of extensive disease (ED), chemotherapy-naive, evaluable or measurable disease, expected survival $\geqslant 2$ months, adequate organ functions (leucocyte count $\geqslant 4000\,\mathrm{mm}^{-3}$, platelet count $\geqslant 100\,000\,\mathrm{mm}^{-3}$, haemoglobin level $\geqslant 9.0\,\mathrm{g\,dl}^{-1}$, AST/ALT $\leqslant 2\times$ upper limit of normal range, total bilirubin $\leqslant 1.5\,\mathrm{mg\,dl}^{-1}$, creatinine $\leqslant 1.5\,\mathrm{mg\,dl}^{-1}$, 24-h creatinine clearance (Ccr) $\geqslant 50\,\mathrm{ml\,min}^{-1}$, and PaO2 $\geqslant 60$ mmHg), no symptomatic pericardial or pleural effusion requiring drainage, no active concomitant malignancy, no senile dementia, and written informed consent. Exclusion criteria included brain metastases requiring radiotherapy, superior vena cava (SVC) syndrome requiring radiotherapy, serious medical or psychiatric illness, or pregnancy or lactation. Staging procedures included chest X-ray, computed tomography (CT) scan of the chest, CT scan or magnetic resonance

imaging (MRI) of the brain, CT scan or ultrasound of the abdomen, isotope bone scanning, and bone marrow aspiration or biopsy.

Treatment protocol

Patients were randomised to either the CE arm or the SPE arm. The CE regimen consisted of carboplatin area under the curve (AUC) of five intravenously (IV) on day 1 and etoposide 80 mg m^{-2} IV on days 1, 2, and 3. The SPE regimen consisted of cisplatin 25 mg m^{-2} IV on days 1, 2, and 3 and etoposide 80 mg m^{-2} IV on days 1, 2, and 3. Cycles were repeated every 3–4 weeks for up to four courses. In our previous phase II study using the CE regimen for elderly patients with SCLC, carboplatin AUC of 5 on day 1 and etoposide 100 mg m^{-2} on days 1, 2, and 3 were administered every 4 weeks (Okamoto *et al*, 1999). However, because grade 3 or 4 neutropenia occurred in 91% of the patients, in the current phase III trial we decided to reduce the etoposide dosage to 80 mg m^{-2} on days 1, 2, and 3, and repeat the cycle every 3–4 weeks instead of every 4 weeks. Twenty-four-hour Ccr was substituted for glomerular filtration rate (GFR) in Calvert's formula. Antiemetic prophylaxis with 5-HT3 antagonists plus dexamethasone was used at the treating physician's discretion. According to the Japanese approved guideline, prophylactic use of recombinant human granulocyte colony-stimulating factor (G-CSF) was recommended for daily administration after day 4 until the leucocyte (neutrophil) count exceeded 10 000 (5000) mm^{-3}. If the leucocyte (neutrophil) count decreased to less than 3000 (1500) mm^{-3}, then G-CSF was restarted. However, the actual use of G-CSF was left at the discretion of the treating physician. Subsequent courses of chemotherapy were initiated when leucocyte count $\geqslant$3000 mm^{-3}; platelet count $\geqslant$75 000 mm^{-3}; Cr$\leqslant$1.5 mg dl^{-1}; AST/ALT$\leqslant$2.5 $\times$ upper limit of normal range; and either PS$\leqslant$2 and age$\geqslant$70 years, or PS$\leqslant$3 and age$<$70 years were satisfied both after day 21 and two or more days after the discontinuation of G-CSF. If the above criteria were not satisfied by the first day of the next course, treatment was withheld until full recovery. If more than 6 weeks passed from day 1 of the last course, the patient was removed from protocol treatment. Dose modifications were made based only on grade 4 haematologic toxicities. If grade 4 leucopenia or neutropenia lasting 4 days or more was present, or grade 4 thrombocytopenia occurred, the doses for the next course were carboplatin AUC of 4 on day 1, cisplatin 20 mg m^{-2} for 3 days, and etoposide 60 mg m^{-2} for 3 days. If the same haematologic toxicity was observed after dose reduction, the patient was removed from protocol treatment. If grade 3 or 4 non-haematologic toxicities, except for nausea/vomiting and hyponatraemia, occurred, the patient was removed from protocol treatment even if the toxicities improved thereafter.

Responders after four courses were not allowed to receive further chemotherapy until progressive disease (PD) developed. Although post-protocol treatment was left at the discretion of the physician, crossover treatment was prohibited.

Evaluation

Tumour responses were evaluated according to World Health Organization criteria (World Health Organization, 1979). Toxicities were evaluated according to JCOG Toxicity Criteria (Tobinai *et al*, 1993), which are similar to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC ver 1) for the grading of toxicities.

Palliation score

Study-specific eight-item palliation scores were completed by patients before treatment and 3 weeks after the third course of chemotherapy. The attending physicians were not allowed to complete the scores. The items consisted of cough, pain, anorexia, shortness of breath, well-being, nausea, diarrhoea or constipation, and sleep. The items were scored as not at all present (0), a little (1), moderate (2), and very much (3). The sum of the total score for all eight items was compared between the baseline and post-treatment assessments. If the post-treatment score was below the baseline score, the palliation score for that patient was judged as having shown improvement.

Study design and statistics

This trial was designed as a multicentre, prospective, randomised phase III trial. The study protocol was approved by the Clinical Trial Review Committee of JCOG and the institutional review board of each participating institution before the initiation of the study. The primary endpoint was overall survival (OS). In this study, the experimental arm was the CE arm and the control was the SPE arm. The MST of our previous phase II trial for elderly patients with extensive disease small-cell lung cancer (ED-SCLC) using the CE regimen was 10.1 months. The MST of the SPE regimen for a similar population was not available at the time of the study proposal. Although Westeel and co-workers in 1998 and Murray and co-workers in 1998 reported an excellent MST of SPE plus concurrent chest radiotherapy for elderly or frail patients with limited disease (LD)-SCLC, an MST of the SPE regimen for elderly or frail patients with ED-SCLC was not available at that time. The only data available on the CAV/PE regimen for elderly or poor-risk patients with SCLC using reduced cisplatin (60 mg m^{-2} IV on day 1) were reported by Souhami and co-workers in 1997 and the MST of that study was 5.9 months. Therefore, for statistical calculations in the current phase III trial, we used the MST value of the Souhami trial for the control arm instead of the MST of the SPE regimen. In addition, an individualised AUC-based dosing strategy of carboplatin was expected to have greater efficacy and less toxicity compared with the SPE regimen at that time. This trial was designed as a superiority trial and the planned sample size was 110 patients in each arm for 80% power to detect a 0.67 hazard ratio for CE to SPE in OS at an alpha of 0.025 (one sided) (Schoenfeld and Richter, 1982). Patients were randomised to receive either CE or SPE with a minimisation method for balancing centre, PS (0–1 *vs* 2–3) and age ($\geqslant$70 years *vs* $<$70 years).

Survival distributions were compared by unstratified log-rank test. Proportion of improvement in palliation score was evaluated by Fisher's exact test. The change in each symptom score by treatment arm was evaluated by the Wilcoxon rank-sum test. The relationship between the interval of each chemotherapy course and the two regimens was evaluated by the Wilcoxon rank-sum test. Multivariate analysis was performed using Cox's proportional hazards model to evaluate the importance of seven clinically selected variables (treatment arm, PS, age, sex, lactate dehydrogenase level, alkaline phosphatase level, and leucocyte count) as prognostic factors. All *P*-values in this report are two sided, excluding *P*-values for OS and progression-free survival (PFS).

The interim analysis was performed after half of the planned number of patients had been enrolled in March 2002, with adjustment for multiplicity by the alpha-spending function (DeMets and Lan, 1994) with an O'Brien-Fleming type boundary. Because the interim analysis did not meet the prespecified stopping criteria, the study was continued and the planned accrual of 220 patients was randomised in this trial.

RESULTS

Patient characteristics

Between August 1998 and February 2004, a total of 220 patients were registered from 24 institutions. Baseline characteristics were well balanced between the arms. Median age was 74 years, 92% were 70 years or older, 88% were male, and 74% had a PS of 0 or 1 (Table 1). One patient in the CE arm was found to have LD after the completion of protocol chemotherapy due to protocol violation, and this patient was considered ineligible (Figure 1).

Delivery of treatment

Reasons for termination of treatment are listed in Figure 1, and there were no major differences between the arms. Of the patients, 63% in the CE arm and 67% in the SPE arm completed four courses, and 11% in the CE arm and 8% in the SPE arm did not complete treatment because of toxicity or complications. Treatment-related death (TRD) occurred in four patients; three patients in the CE arm and one in the SPE arm. All TRDs of patients who were ⩾70 years old with a good pretreatment PS (all PS 1) were associated with neutropenic infection, which occurred after the first course of chemotherapy. Although the median interval of chemotherapy was slightly more prolonged in the CE arm than in the SPE arm, total delivered courses were similar between the arms (Table 2). One patient in the SPE arm never received chemotherapy due to the occurrence of delirium after registration. Dose reduction was more frequently observed in the CE arm than in the SPE arm: 29% *vs* 10%, $P<0.01$. Course delay, G-CSF delivery and total courses with G-CSF delivery were similar between the arms.

Toxicity and palliation score

Toxicities are listed in Table 3. Grade 3 or 4 leucopenia and neutropenia occurred in 54 and 95% of the CE arm *vs* 51 and 90% of the SPE arm, respectively. Grade 3 or 4 thrombocytopenia occurred more frequently in the CE arm than in the SPE arm: 56 *vs* 16%, $P<0.01$. Gastrointestinal toxicities including nausea or vomiting and diarrhoea were mild in both arms. There were few grade 3 or 4 toxicities and no remarkable differences between the arms. Other non-haematologic toxicities were similarly distributed between the arms. Grade 3–4 hyponatraemia, mainly caused by syndrome of inappropriate antidiuretic hormone (SIADH) secretion, occurred in 14–16% of the patients. More importantly, thrombocytopenia occurred more frequently in the CE arm, but none of the patients in either arm showed grade 3 or 4 bleeding. Only one patient in the CE arm showed grade 2 bleeding. Because no grading of febrile neutropenia was listed in JCOG toxicity criteria, the rate of the toxicity was not investigated in this study.

Baseline and post-treatment palliation scores were evaluated in 220/220 (100%) and 208/220 (95%) patients, respectively. We handled missing values by imputing the worst score. Improvement was achieved in 69 (63%) patients in the CE arm *vs* 61 (56%) patients in the SPE arm, although the difference was not statistically significant ($P=0.34$). Similarly, there were no statistical differences in the change of each symptom score between the arms (Table 4).

Objective tumour response, PFS and OS

The objective response rate of 73% was quite similar between the arms. Five CRs and 75 PRs were observed in each arm (Table 5). Progression-free survival curves and OS curves are shown in Figure 2A and B. Ninety-seven percent of the patients had progressed or died at the time of final analysis. Progression-free survival was quite similar between the arms ($P=0.20$, one sided).

Table 1 Patient characteristics

	CE ($n=110$)	SPE ($n=110$)	*P*-value
Age (years)			
Median (range)	74 (56–86)	73.5 (55–85)	0.34
⩾70 years old (%)	102 (93)	100 (91)	0.81
Sex (male/female)	95/15	98/12	0.68
ECOG PS, 0–1/2/3	81/21/8	81/19/10	0.80
⩾5% weight loss	26	38	0.18
LN metastasis			
Contralateral mediastinum	71	59	0.13
Supraclavicular	89	79	0.15
Distant metastasis			
Liver	30	30	1.0
Lung	31	30	1.0
Brain	18	18	1.0
Bone	25	17	0.23
Adrenal	13	7	0.24
Bone marrow	12	12	1.0

CE, carboplatin plus etoposide; ECOG, Eastern Cooperative Oncology Group; LN, lymph node; PS, performance status; SPE, split doses of cisplatin plus etoposide.

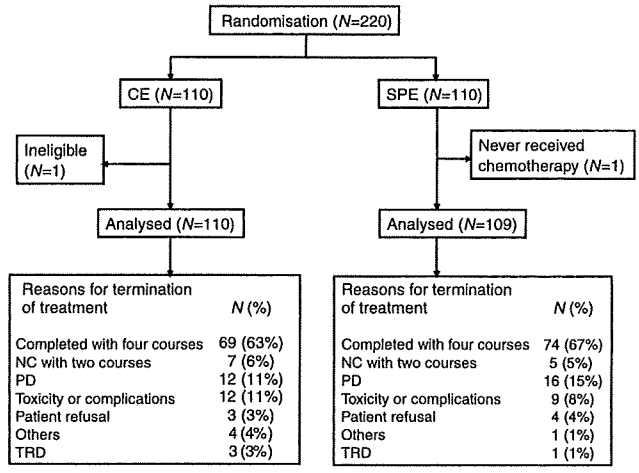

Figure 1 Flow diagram of randomised phase III trial of CE *vs* SPE in elderly or poor-risk patients with extensive disease SCLC.

Table 2 Compliance and drug delivery

	CE ($n=110$)	SPE ($n=109$[a])	*P*-value
Median interval of each chemotherapy (days) (range)			
1–2	27 (14–35)	23 (20–37)	0.02[b]
2–3	25 (21–56)	22 (20–35)	0.07[b]
3–4	27 (21–36)	24 (21–38)	0.05[b]
Total delivered courses/projected courses	353/440 (80%)	360/436 (83%)	
Dose reduction	32 (29%)	11 (10%)	<0.01[c]
Course delay	45 (41%)	40 (37%)	0.58[c]
G-CSF delivery	81 (74%)	84 (77%)	0.64[c]
No. of courses with G-CSF delivery/number of total courses	183/354 (52%)	203/362 (56%)	

CE, carboplatin plus etoposide; G-CSF, granulocyte colony-stimulating factor; SPE, split doses of cisplatin plus etoposide. [a]One patient never received chemotherapy due to delirium after registration. [b]Wilcoxon rank-sum test. [c]Fisher's exact test.

Table 3 Toxicities (JCOG Toxicity Criteria, Worst Grade of Any Course)

	CE					SPE					
	Grade					Grade					
Toxicity	**1**	**2**	**3**	**4**	**3+4 (%)**	**1**	**2**	**3**	**4**	**3+4 (%)**	***P*-value**
Haematologic											
Leucopenia	5	45	46	13	(54)	8	43	49	7	(51)	0.79
Neutropenia	0	5	46	58	(95)	4	7	41	57	(90)	0.22
Anaemia	9	58	32	—	(29)	20	45	27	—	(25)	0.54
Thrombocytopenia	20	18	29	32	(56)	16	15	12	5	(16)	<.01
Non-haematologic											
Nausea/vomiting	40	24	2	—	(2)	46	28	3	—	(3)	0.68
Diarrhoea	8	9	1	0	(1)	11	3	1	0	(1)	1.0
Bilirubin	—	31	0	0	(0)	—	16	1	0	(1)	0.50
AST	47	9	3	0	(3)	30	8	6	0	(6)	0.33
ALT	40	9	2	0	(2)	38	8	4	0	(4)	0.45
Creatinine	10	2	0	0	(0)	27	3	1	0	(1)	0.50
Hyponatraemia	38	11	7	11	(16)	46	20	6	9	(14)	0.58
PaO2	39	21	7	1	(10)	44	23	2	1	(4)	0.22
Fever	15	15	0	0	(0)	21	16	0	0	(0)	—
Infection	12	15	5	3	(7)	16	7	5	1	(6)	0.78
Bleeding	8	1	0	0	(0)	4	0	0	0	(0)	—
Neurologic-sensory	2	1	0	—	(0)	3	2	0	—	(0)	—
Alopaecia	67	22	—	—		66	15	—	—		

CE, carboplatin plus etoposide; JCOG, Japan Clinical Oncology Group; PaO_2, partial pressure of oxygen; SPE, split doses of cisplatin plus etoposide.

Table 4 Palliation score

	CE		SPE		
	Change from baseline		Change from baseline		
Symptom	**Mean (s.d.)**	**Median (range)**	**Mean (s.d.)**	**Median (range)**	***P*[a]**
Cough	−0.38 (1.16)	0 (−3 to 3)	−0.54 (1.06)	0 (−3 to 3)	0.51
Pain	−0.19 (1.00)	0 (−3 to 3)	−0.19 (0.96)	0 (−3 to 3)	0.96
Anorexia	−0.07 (1.16)	0 (−3 to 3)	0.08 (1.22)	0 (−3 to 3)	0.37
Shortness of breath	−0.05 (1.02)	0 (−2 to 3)	−0.31 (0.95)	0 (−3 to 3)	0.12
Well-being	−0.15 (1.13)	0 (−3 to 3)	−0.02 (1.14)	0 (−3 to 3)	0.48
Nausea	0.16 (0.84)	0 (−2 to 3)	0.26 (0.80)	0 (−1 to 3)	0.21
Diarrhoea or constipation	0.05 (1.07)	0 (−3 to 3)	0.04 (0.99)	0 (−3 to 3)	0.69
Sleep	−0.15 (1.08)	0 (−3 to 3)	−0.04 (0.89)	0 (−3 to 2)	0.10
Total	−0.80 (6.04)	−2 (−12 to 22)	−0.71 (5.35)	−1 (−15 to 21)	0.32

CE, carboplatin plus etoposide; s.d., standard deviation; SPE, split doses of cisplatin plus etoposide. [a]Wilcoxon rank-sum test.

The MST was 5.2 months in the CE arm *vs* 4.7 months in the SPE arm. OS was very similar between the arms ($P=0.54$, one sided). The MST and 1-year survival rate was 10.6 months and 41% in the CE arm *vs* 9.9 months and 35% in the SPE arm.

Second-line chemotherapy

According to an *ad-hoc* survey (not pre-specified in the protocol), 130 (59%) patients (68 (62%) patients in the CE arm and 62 (56%) in the SPE arm) received second-line chemotherapy after relapse and the regimens were almost equally distributed between the arms. The same regimen as the initial chemotherapy, platinum-based combinations, and irinotecan regimens with or without other agents were administered in 17 (15%), 48 (44%), and 40 (36%) patients in the CE arm *vs* 10 (9%), 44 (40%), and 40 (36%) in

Table 5 Therapeutic response (WHO)

	CE	SPE	Total
CR	5	5	10
PR	75	75	150
NC	17	11	28
PD	11	16	27
NE	2	3	5
Total	110	110	220
Response rate	73%	73%	
95% CI	63–81%	63–81%	

CE, carboplatin plus etoposide; CI, confidence interval; CR, complete response; NC, no change; NE, not evaluable; PD, progressive disease; PR, partial response; SPE, split doses of cisplatin plus etoposide; WHO, World Health Organization.

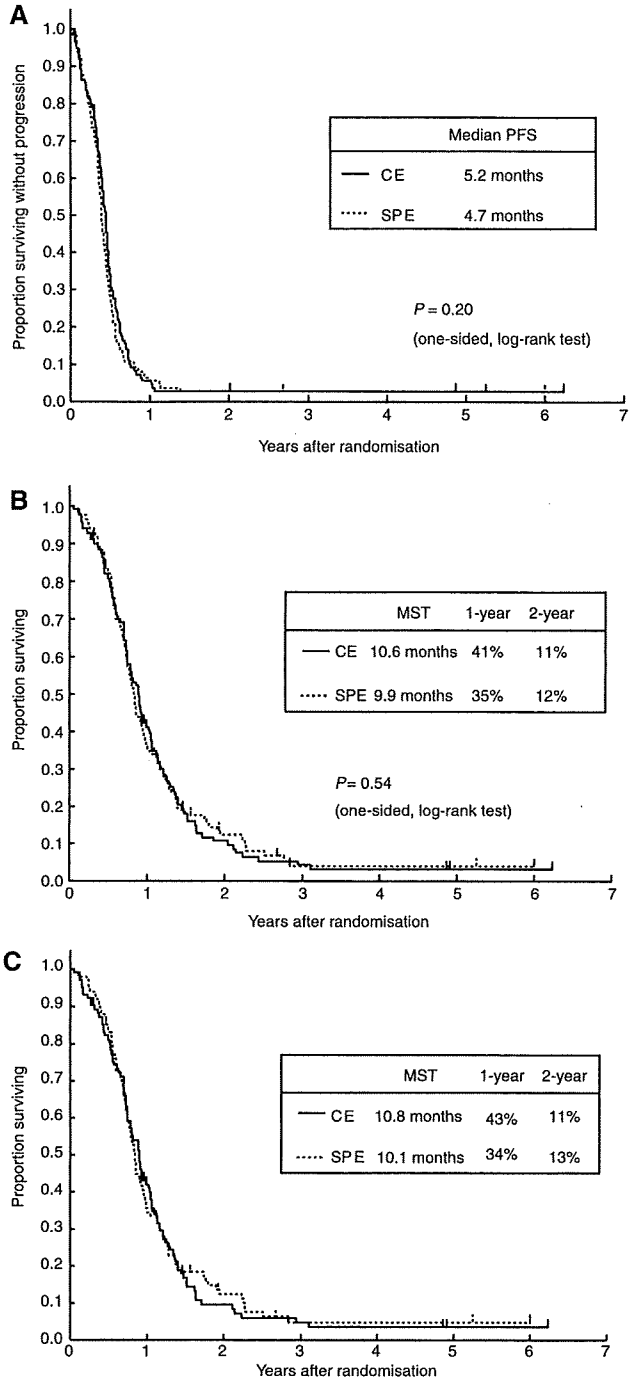

Figure 2 (**A**) PFS curves ($n=220$). (**B**) OS curves ($n=220$). (**C**) Survival curves of the patients ⩾70 years of age with a PS of 0–2 ($n=202$).

the SPE arm. Other chemotherapy regimens included topotecan monotherapy, amrubicin monotherapy, or other regimens.

Subset analysis and multivariate analysis

Subset analysis was performed according to PS and age (Table 6). There were no differences in OS between the arms in any subset; thus, an interaction between treatment and PS is unlikely. The survival curves of the patients ⩾70 years of age with a PS of 0–2 are shown in Figure 2C, and the survival curves were very similar with that of original overall populations. Even in the multivariate analysis with seven selected baseline variables, there was no difference in OS between the arms. High lactate dehydrogenase level was most strongly associated with poor prognosis (Table 7).

Table 6 Subset analysis – overall survival

Subgroup	Number of patients (%)	MST (months) CE	MST (months) SPE
PS 0–1	162 (74)	10.9	10.1
PS 2–3	58 (26)	8.3	8.1
<70 years and PS 3	18 (8)	7.1	6.9
⩾70 years and PS 0–2	202 (92)	10.8	10.0

CE, carboplatin plus etoposide; MST, median survival time; PS, performance status; SPE, split doses of cisplatin plus etoposide.

Table 7 Multivariate analysis with baseline prognostic factors

Variables	*P*-value	Hazard ratio	95% CI
Treatment arm (CE vs. SPE)	0.99	0.99	0.75–1.33
Alkaline phosphatase level (normal *vs* abnormal)	0.97	0.99	0.68–1.46
Lactate dehydrogenase level (⩾ × 1.5 *vs* < × 1.5)	<0.001	1.69	1.23–2.26
Leucocyte count (⩾10 000/mm^3 *vs* <10 000/mm^3)	0.06	1.82	0.99–3.36
Age (⩾75 years *vs* <75 years)	0.77	1.05	0.78–1.41
PS (2–3 *vs* 0–1)	0.41	1.15	0.82–1.61
Sex (female *vs* male)	0.13	0.70	0.45–1.11

CE = carboplatin plus etoposide; SPE = split doses of cisplatin plus etoposide; PS = performance status; CI = confidence interval.

DISCUSSION

Until recently, there was no standard chemotherapeutic regimen for elderly SCLC patients. Two phase III (Medical Research Council Lung Cancer Working Party, 1996; Souhami *et al*, 1997) and two randomised phase II trials (Pfeiffer *et al*, 1997; Ardizzoni *et al*, 2005) have shown that suboptimal chemotherapies, such as oral etoposide monotherapy or attenuated doses of combination chemotherapy, may lead to reduced survival in elderly or poor-risk SCLC patients when compared with standard doses of combination chemotherapies. The CE regimen, which has acceptable toxicities and reproducible efficacy, has been used in elderly or poor-risk patients with SCLC worldwide, although there have been substantial differences in toxicities and efficacy between the reported phase II trials. Four trials demonstrated both favourable toxicities and efficacy (Carney, 1995; Evans *et al*, 1995; Matsui *et al*, 1998; Okamoto *et al*, 1999) and three showed somewhat disappointing results because of suboptimal doses of oral etoposide (Larive *et al*, 2002), greater inclusion of patients with poor prognostic factors (Samantas *et al*, 1999), and deterioration of comorbidities as a result of chemotherapy (Quoix *et al*, 2001). No phase III trial evaluating the role of the CE regimen in this population has been reported until now.

This is the first phase III trial comparing carboplatin-based CE and cisplatin-based SPE regimens in elderly or poor-risk patients with ED-SCLC. In addition, this is also the largest randomised trial specifically designed for elderly or poor-risk SCLC patients. Although there was no significant difference in the palliation scores, response rate, and OS between the arms, the efficacy of

both regimens was promising, as this study included only elderly or poor-risk patients with SCLC. Most toxicities were tolerable and the treatment compliance was also favourable in both arms. Approximately two-thirds of the patients received all four cycles of treatment. The CE arm in the current trial had more pronounced thrombocytopenia, which was considered manageable because none of the patients in the CE arm showed grade 3 or 4 bleeding, and the CE arm had a slightly prolonged course interval and a slightly greater incidence of dose reduction. However, in our opinion, these toxicities are less meaningful in clinical practice. More importantly, the CE regimen does not require hydration and can be given in an outpatient setting. Based on the results of this study, many JCOG members prefer the CE regimen to the SPE regimen and consider it to be more suitable for the control arm of future phase III trials.

The MST of each regimen (10.6 months for CE *vs* 9.9 months for SPE) was promising considering that this study included only elderly or frail patients with ED-SCLC. However, some retrospective studies have shown that fit elderly patients who have adequate organ functions, a good PS, and no comorbidity are able to tolerate intensive chemotherapy well and show a similar therapeutic response and survival rate as younger patients (Siu *et al*, 1996; Yuen *et al*, 2000). In fact, in this trial the MST of fit elderly patients $\geqslant$70 years of age with a PS of 0–1 was 10.9 months for the CE arm and 10.1 months for the SPE arm. In contrast, the MST of patients with a PS of 3 was only approximately 7 months. Furthermore, the group of fit elderly patients comprised 74% of the patients in this study. Therefore, the favourable survival rates in our trial may be attributable to patient selection. In other words, one limitation of this study is that the results of this trial cannot be extrapolated to frail elderly with a poor PS and/or comorbid illness because of the likelihood of greater inclusion of fit elderly patients in this trial.

Although the total dose in both the CE and SPE arms was slightly lower than the standard regimen, 92% of the patients showed grade 3 or 4 neutropenia, and dose reduction and course delay occurred frequently. However, the MST of both regimens was comparable with that of non-elderly or non-selected patients with ED-SCLC in historical reports (Noda *et al*, 2002; Niell *et al*, 2005). These findings suggest that both regimens are not suboptimal, but are near-full and effective doses for elderly or poor-risk patients with ED-SCLC. The CE arm in the current trial had a slightly prolonged course interval and a slightly greater incidence of dose reduction when compared to the SPE regimen. However, 95% of the patients showed grade 3 or 4 neutropenia and 56% showed grade 3 or 4 thrombocytopenia. Therefore, we believe that the dose escalation of the CE regimen may be difficult in this trial.

It remains unclear whether the elderly are able to tolerate a single modest dose of cisplatin (60–80 mg m^{-2} IV) on day 1. We feel that a fit elderly person who passes strict eligibility criteria can receive a modest dose of cisplatin IV on day 1. However, the more common situation is of elderly patients who have comorbidity and a poor PS, and cannot tolerate a standard single dose of cisplatin. Westeel *et al* (1998) and Murray *et al* (1998) reported that split doses of cisplatin were safely and effectively administered in elderly or frail patients with LD-SCLC. The SPE regimen appeared to be an appropriate treatment for elderly patients with SCLC who cannot tolerate a standard single dose of cisplatin. However, it remains unclear whether fit elderly patients in our trial can tolerate a standard single dose of cisplatin, and if so, it also remains unclear whether fit elderly patients who receive a standard single dose of cisplatin are able to achieve a more improved survival than those who receive SPE. Unfortunately, no randomised study comparing a single standard dose of cisplatin with SPE has been reported in fit elderly patients with SCLC.

There are some problems with the design in this study. The hypothesis was that carboplatin would improve survival, and the design of the trial was a superiority design with survival as the primary end point. However, this hypothesis was based on two possible misconceptions. First, carboplatin could be better dosed and might be more efficacious than cisplatin in SCLC. Unfortunately, this hypothesis could not be sustained on the basis of the available literatures. A number of clinical trials have indicated that carboplatin-based combination chemotherapy has a similar or slightly reduced efficacy compared with cisplatin-based combination chemotherapy against various tumours (Go and Adjei, 1999; Hotta *et al*, 2004). Therefore, our trial should have been designed as a non-inferiority trial. However, if this trial were planned as a non-inferiority trial, a total sample size would be about 500 to 1000 patients, with equal expected survival and a non-inferiority margin for hazard ratio ranging from 1.2 to 1.3. Second, the cisplatin dose in the control arm was an attenuated dose. Souhami *et al* (1997) used reduced dose of cisplatin (60 mg m^{-2} IV on day 1) and Murray *et al* (1998) used a single course of a split cisplatin dose in their studies. These regimens were completely different from the control arm in the present study. A standard dose of cisplatin given in 3 days is the best way of giving standard cisplatin (30 mg m^{-2} IV on days 1–3) with etoposide (130 mg m^{-2} IV on days 1–3), according the North Central Cancer Treatment Group (Maksmiuk *et al*, 1994). Had standard SPE been used for the control arm, better survival might have been achieved with increased toxicities. Another problem with the design was the inclusion of patients with a PS of 3, even if they were less than 70 years old. This made the target population heterogeneous. The number of such patients actually recruited was quite small, so emphasising the inappropriateness of their inclusion. A further limitation of this study may be a long accrual period of five-and-a-half years. Because our oncologists might have been afraid of the risk of TRD or increased toxicities in frail elderly with a poor PS and/or comorbid illness, more fit elderly patients were selectively registered and consequently the accrual rate was very slow.

In our trial, although both regimens were well-tolerated and efficacy was promising, over 90% of the patients in both arms showed grade 3 or 4 neutropenia, which may be justified and acceptable for a clinical trial involving elderly or poor risk patients with ED-SCLC, because only 6% of the patients showed grade 3 or 4 infection and TRD occurred in only four (1.8%) patients. Because all TRD occurred after the first course of chemotherapy, careful monitoring and management is necessary, particularly in the first course, if CE or SPE are administered to elderly or frail patients. Several retrospective analyses (Findlay *et al*, 1991; Radford *et al*, 1992) and a prospective study (Timmer-Bonte *et al*, 2005) have shown that standard-dose chemotherapy without G-CSF support causes more risk of early death and sepsis in the older population. Moreover, the American Society of Clinical Oncology (ASCO) guideline recommends the use of prophylactic G-CSF in patients at higher risk for chemotherapy-induced infection, such as those having a poor PS, older age, or comorbid illness (Smith *et al*, 2006). In this trial, the prophylactic use of G-CSF was recommended, but the actual use was left to the discretion of the treating physician because the use of G-CSF leads to increased drug cost. Although G-CSF was administered in only 54% of the total courses, we believe that the prophylactic use of G-CSF with CE regimen should be recommended in a new trial or clinical practice.

In conclusion, although the SPE regimen is still considered to be the standard treatment for elderly or poor-risk patients with ED-SCLC, the CE regimen can be an alternative for this population considering the risk-benefit balance. Based on the results of our trial, a phase III trial of the CE regimen *vs* amrubicin monotherapy, supported by a pharmaceutical company, is now ongoing in elderly patients with ED-SCLC in Japan, and a comparative trial of the CE regimen *vs* carboplatin plus irinotecan regimen (Okamoto *et al*, 2006) is being discussed for a future trial in our group.

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Appendix

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Clinical Studies

A phase-II trial of dose-dense chemotherapy in patients with disseminated thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9605)

H Kunitoh[*,1,9], T Tamura[1], T Shibata[2], K Nakagawa[3], K Takeda[4], Y Nishiwaki[5], Y Osaki[6], K Noda[7], A Yokoyama[8], N Saijo[3,10] and JCOG Lung Cancer Study Group, Tokyo, Japan

[1]Department of Medical Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; [2]JCOG Data Center, Center for Cancer Control and Information Services, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; [3]Department of Medical Oncology, Kinki University School of Medicine, 377-2 Ohnohigashi, Osakasayama, Osaka 589-8511, Japan; [4]Department of Medical Oncology, Osaka City General Hospital, 2-13-22 Miyakojima-Hondori, Miyakojima-ku, Osaka 534-0021, Japan; [5]Department of Thoracic Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanohara, Kashiwashi, Chiba 277-8577, Japan; [6]Department of Internal Medicine, Asahikawa Medical College, 1-1-1 Higashinijou, Midorigaoka, Asahikawa, Hokkaido 078-8510, Japan; [7]Division of Thoracic Oncology, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama, Kanagawa 241-0815, Japan; [8]Department of Medical Oncology, Niigata Cancer Center, 2-15-3, Kawagishi-cho, Niigata-shi, Niigata 951-8566, Japan; [9]Department of Respiratory Medicine, Mitsui Memorial Hospital, 1 Kandaizumicho, Chiyoda-ku, Tokyo 101-8643, Japan; [10]National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwashi, Chiba 277-8577, Japan

BACKGROUND: To evaluate the safety and efficacy of dose-dense weekly chemotherapy in the treatment of advanced thymoma.

METHODS: Subjects comprised patients with histologically documented chemotherapy-naïve thymoma with stage-IVa or IVb disease. Thymic carcinoma, carcinoid or lymphoma cases were excluded. Patients received 9 weeks of chemotherapy: cisplatin (25 mg m^{-2}) on weeks 1–9; vincristine (1 mg m^{-2}) on weeks 1, 2, 4, 6 and 8; and doxorubicin (40 mg m^{-2}) and etoposide (80 mg m^{-2}) on days 1–3 of weeks 1, 3, 5, 7 and 9. Chemotherapy courses were supported by granulocyte colony-stimulating factor. Post-protocol local therapy was allowed.

RESULTS: From July 1997 to March 2004, 30 patients were entered. Three were ineligible due to different histology. Chemotherapy-associated toxicity was mainly haematological and was well tolerated, with no deaths due to toxicity, and 87% of patients completed the planned 9-week regimen. Overall response rate was 59%, with 16 of the 27 eligible patients achieving partial response. Median progression-fee survival (PFS) was 0.79 years (95% confidence interval: 0.52–1.40 years), and PFS at 1 and 2 years was 37 and 15%, respectively. Overall survival rates at 2 and 5 years were 89 and 65%, respectively.

CONCLUSION: In stage-IV thymoma patients, weekly dose-dense chemotherapy offers similar activity to conventional regimens.

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Thymoma is a rare thoracic tumour, but remains one of the most common tumours originating in the mediastinum (Thomas *et al*, 1999; Giaccone, 2005; Girard *et al*, 2009). Clinical behaviour tends to be indolent, but dissemination into the pleural space eventually occurs and sometimes distant metastasis arise (Thomas *et al*, 1999). Thymoma is frequently associated with paraneoplastic syndromes such as myasthenia gravis or pure red cell aplasia (Thomas *et al*, 1999; Giaccone, 2005). No International Union Against Cancer (UICC) TNM classification is available, and the Masaoka classification has been widely used for clinical staging (Masaoka *et al*, 1981; Girard *et al*, 2009).

*Correspondence: Dr H Kunitoh; E-mail: hkkunito@mitsuihosp.or.jp
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The majority of thymomas are discovered at a limited stage, representing Masaoka stage-I or II, and surgical resection is the treatment of choice for such cases (Thomas *et al*, 1999; Giaccone, 2005; Girard *et al*, 2009). Even when the tumour invades neighbouring organs, as stage-III disease, surgical resection with postoperative radiotherapy is the preferred treatment when complete resection can be achieved (Curran *et al*, 1988; Urgesi *et al*, 1990; Ogawa *et al*, 2002; Strobel *et al*, 2004).

Systemic chemotherapy is usually used for stage-IVa (with pleural or pericardial dissemination) or stage-IVb disease (with lymphogenous or haematogenous metastases), but optimal management is less well established (Thomas *et al*, 1999; Girard *et al*, 2009). Several reports have described favourable outcomes in limited numbers of patients with stage-IVa disease treated using multimodal treatment including surgery (Kim *et al*, 2004; Yokoi *et al*, 2007).

Conversely, thymomas are generally reported to be chemotherapy-sensitive tumours, with response rates of 50–70% to

combination chemotherapy (Fornasiero *et al*, 1990; Loehrer *et al*, 1994, 1997, 2001; Giaccone *et al*, 1996; Berruti *et al*, 1999; Kim *et al*, 2004; Lucchi *et al*, 2006; Yokoi *et al*, 2007). Active agents include cisplatin (CDDP), vincristine (VCR), doxorubicin (ADM), etoposide (ETP), cyclophosphamide (CPM) and ifosfamide (IFX). Recent reports have shown marginal activity of pemetrexed (Loehrer *et al*, 2006) and combined carboplatin and paclitaxel (Lemma *et al*, 2008).

Dose-dense chemotherapy with the CODE combination (CDDP–VCR–ADM–ETP) and addition of granulocyte colony-stimulating factor (G-CSF) can be safely administered to patients with advanced lung cancer (Murray *et al*, 1991; Fukuoka *et al*, 1997). Theoretically, this approach might be suitable for chemosensitive tumours such as small-cell lung cancer and thymoma (Goldie and Coldman, 1983, 1984; Levin and Hryniuk, 1987; Murray, 1987). Because some pilot data in Japan suggested that administration of 12 weeks of the CODE chemotherapy was barely feasible, subsequent Japanese trials used a modified schedule, which was shortened to 9 weeks (Fukuoka *et al*, 1997; Furuse *et al*, 1998).

In 1996, the Japan Clinical Oncology Group (JCOG) initiated two clinical trials for advanced thymoma: one aimed at evaluating the safety and efficacy of the CODE regimen in stage IV, disseminated thymoma (JCOG 9605), and the other aimed at evaluating the safety and efficacy of CODE combination chemotherapy followed by surgical resection and postoperative radiotherapy in initially unresectable stage-III thymoma (JCOG 9606). The primary endpoint in each study was progression-free survival (PFS). The results of JCOG 9605 are reported herein.

PATIENTS AND METHODS

Eligibility criteria

Patients with chemotherapy-naive, histologically documented thymoma at Masaoka stage IVa or IVb were eligible for entry into the study. Thymoma must have been confirmed histologically and thymic tumours with other histology, such as thymic carcinoma, carcinoid or lymphoma, were excluded. Each patient was required to fulfil the following criteria: age, 15–70 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS), 0–2; adequate organ function, that is, leukocyte count $\geqslant 4000\,\mu l^{-1}$, platelet count $\geqslant 10^5\,\mu l^{-1}$, hemoglobin $\geqslant 10.0\,g\,dl^{-1}$, serum creatinine <1.5 mg dl^{-1}, creatinine clearance $\geqslant 60$ ml min^{-1}, serum bilirubin <1.5 mg dl^{-1}, serum alanine transaminase and aspartate transaminase levels less than double the upper limit of the institutional normal range; and PaO_2 $\geqslant 70$ mm Hg. Exclusion criteria included uncontrolled heart disease, uncontrolled diabetes or hypertension, pulmonary fibrosis or active pneumonitis as evidenced on chest radiography, infections necessitating systemic use of antibiotics, disease necessitating emergency radiotherapy such as superior vena cava obstruction syndrome, active concomitant malignancy and women who were pregnant or lactating. Also excluded were those patients with grave complications of thymoma, such as pure red cell aplasia or hypogammaglobulinemia. Myasthenia gravis was allowed and these patients were not excluded *per se*.

Patient eligibility was confirmed by the JCOG Data Center before patient registration. This study protocol was approved by the institutional review board at each participating centre and written informed consent was obtained from all patients prior to enrolment.

Treatment Plan

Chemotherapy Patients received the 9-week CODE combination chemotherapy as described below. Each chemotherapeutic agent was administered intravenously.

Week 1: CDDP 25 mg m^{-2} on day 1 with antiemetics and ample hydration; VCR (1 mg m^{-2}) on day 1; ADM (40 mg m^{-2}) on day 1 and ETP (80 mg m^{-2}) on days 1–3.

Weeks 2, 4, 6 and 8: CDDP (25 mg m^{-2}) on day 1 with antiemetics and ample hydration and VCR (1 mg m^{-2}) on day 1.

Weeks 3, 5, 7 and 9: CDDP (25 mg m^{-2}) on day 1 with antiemetics and ample hydration, ADM (40 mg m^{-2}) on day 1 and ETP (80 mg m^{-2}) on days 1–3.

Each week, G-CSF (filgrastim ($50\,\mu g\,m^{-2}\,day^{-1}$) or lenograstim ($2\,\mu g\,kg^{-1}\,day^{-1}$)) was administered by subcutaneous injection, except on days when chemotherapy was administered or when leukocyte count was $\geqslant 10\,000\,\mu l^{-1}$. Corticosteroid was used only as part of the antiemetic regimen, and the specific drug and dosage were not regulated by the protocol.

Dose and schedule modifications were performed as follows: when leukocyte count decreased to $<2{,}000\,\mu l^{-1}$ or platelet count decreased to $<50\,000\,\mu l^{-1}$, chemotherapy was delayed by 1 week. If PS decreased to 3–4 or temperature reached $\geqslant 38.0°C$, therapy was likewise delayed for 1 week. No dose modification of chemotherapy drugs was adopted for toxicity.

Post-protocol therapy

Surgery or radiotherapy was allowed after the completion of chemotherapy, at the discretion of the attending physician, even in the absence of apparent tumour regrowth. Conversely, additional chemotherapy without evidence of disease progression was not allowed.

Post-treatment after disease progression was not limited by the study protocol.

Patient evaluation and follow-up

Before enrolment into the study, each patient underwent complete medical history taking and physical examination (including neurological check-up for signs of myasthenia gravis), determination of blood cell counts, serum biochemistry testing, arterial blood gas analysis, pulmonary function testing, electrocardiography, chest radiography, computed tomography (CT) of the chest, CT or ultrasonography of the upper abdomen, whole-brain CT or magnetic resonance imaging (MRI) and an isotope bone scan. Blood-cell counts, serum biochemistry testing and chest radiography were performed weekly during each course of chemotherapy.

The toxicity of chemotherapy was evaluated according to the JCOG Toxicity Criteria (Tobinai *et al*, 1993), modified from version 1 of the National Cancer Institute Common Toxicity Criteria (NCI-CTC). Tumour responses were assessed radiographically according to the standard, two-dimensional WHO criteria (Miller *et al*, 1981), and were classified as complete response (CR), partial response (PR), no change (NC), progressive disease (PD) or non-evaluable (NE). After completion of the protocol therapy, patients were followed up with periodic re-evaluation, including chest CT every 6 months for the first 2 years and annually thereafter.

Central review

Radiographic reviews for the eligibility of enrolled patients and clinical responses were performed at the time of the study group meeting, held every 3–4 months. The study coordinator (H Kunitoh) and a few selected investigators from the group reviewed the radiographic films. The clinical response data presented below were all confirmed by this central review. Reviews of pathological specimens were not performed, because of insufficient logistics of the study group at the time of the study activation in 1997.

Endpoints and statistical considerations

The primary endpoint in each study was PFS. Due the rarity of the tumour and the accrual reported in US trials, which required 10 years to register 26 patients with locally advanced (stage-III) disease (Loehrer *et al*, 1997) and 9 years for 31 patients with disseminated (stage-IV) disease (Loehrer *et al*, 1994), we presumed we would be capable of accruing 30 patients in the target accrual period of 4 years. The sample size was, therefore, not determined based on statistical calculations. The expected PFS for the JCOG 9605 study was 2 years, which would give a 95% confidence interval of 1.3–3.0 years with 30 cases.

The initial study design thus envisioned enrolment of 30 fully eligible cases over 3 years for the study, with a follow-up period of 2 years.

Secondary endpoints included toxicity and safety, objective tumour response to chemotherapy, pattern of relapse, and overall survival (OS).

Progression-free survival and OS were calculated from the date of enrolment and estimated using the Kaplan–Meier method. Progression-free survival was censored at the last date verifiable as progression-free, and OS was censored as of the date of last follow-up. During the accrual period, an interim analysis for futility was planned after half of the patients had been registered and followed for $\geqslant 3$ months. All analyses were performed using SAS software version 8.2/9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

A total of 30 patients from seven institutions were enrolled from July 1997 to March 2004. Three patients were later found ineligible due to wrong histology, with two cases of thymic carcinoma and one case of carcinoid. These mistakes occurred due to technical problems in the patient registry. Since the ineligible cases did receive the protocol therapy, all 30 patients were analysed for characteristics and toxicity. Twenty-seven eligible patients were analysed for clinical response and survival (PFS and OS). Patient characteristics are shown in Table 1.

Table 1 Patient characteristics

Item	
Sex	
Male/female	16/14
Age (years)	
Median/range	47.5/29–69
ECOG performance status	
PS0/PS1/PS2	11/18/1
Masaoka stage	
IVa/IVb	22/8
Smoking history	
No	9
Yes (median pack–years)	21 (22)
Myasthenia gravis	
No/yes	28/2
Histology: thymoma and eligible	27
Lymphocyte predominance	12
Mixed cell	9
Epithelioid cell	4
Clear cell	1
Spindle cell	0
Unclassified	1
Histology: not thymoma (ineligible)	3
Carcinoma	2
Carcinoid	1
Lymphoma	0
Prior therapy	
None	26
Surgery	2
Surgery and radiation	2

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status.

Chemotherapy delivery and toxicity

Nine weeks of chemotherapy were performed for 26 of the original 30 patients (87%). The other four patients included one patient receiving 7 weeks, two receiving 6 weeks and one receiving 3 weeks of therapy. Median duration of chemotherapy for the 26 patients who underwent the planned nine cycles was 10 weeks (range, 9–12 weeks).

Table 2 summarises the major toxicities of chemotherapy, which were mainly haematological. Although 70% of patients experienced grade-IV neutropenia, this was generally transient and rarely complicated by infection/fever. Overall, toxicities were well tolerated and no deaths due to toxicity occurred.

Table 2 Toxicity of chemotherapy ($n = 30$)

Toxicity	Grades 1/2	Grade 3	Grade 4	%Grade 3/4
Leukopenia	3/6	12	8	67
Neutropenia	3/1	5	21	87
Anemia	0/5	25	ND	83
Thrombocytopenia	4/6	5	3	27
ALT	9/0	0	0	0
Creatinine	2/1	0	0	0
PaO_2	9/2	0	0	0
Emesis	13/11	2	ND	7
Diarrhoea	4/2	0	0	0
Stomatitis	4/3	0	0	0
Constipation	3/4	2	0	7
Neuropathy	11/2	0	ND	0
Infection	3/4	3	0	10

Abbreviations: ALT = alanine transaminase; ND = not defined (the JCOG toxicity criteria did not define grade IV in these toxicities).

Other and late complications

Four patients showed thymoma-related complications. One patient suffered from myasthenia gravis crisis occurring during chemotherapy, but subsequently recovered. Another patient showed newly diagnosed myasthenia gravis 2.5 years after completion of the protocol therapy, and thymectomy and resection of the residual tumour were performed. Two other cases had pure red cell aplasia occurring later in the clinical course with disease progression of the thymomas.

Clinical response to chemotherapy

Clinical responses of the 27 eligible patients to chemotherapy were judged radiologically and confirmed by central review. Responses were as follows: CR, 0 patients; PR, 16 patients; NC, 10 patients and PD, 1 patient. Overall response rate was 59% (95% confidence interval, 39–78%).

Post-protocol therapy

Post-protocol local therapy was administered to 18 of the 27 eligible patients (67%). Eight patients (all with stage-IVa disease) underwent surgical resection and 13 patients (nine with stage-IVa disease and four with stage-IVb disease) received thoracic radiotherapy, with three patients receiving both. Whether patients received local therapy after disease progression was not recorded on case report forms.

After disease progression, 16 of the 27 patients (59%) received additional chemotherapy. Post-protocol chemotherapy included platinum re-challenge, irinotecan, taxanes and investigational agents. Clinical response data to those therapies are not available.

PFS and OS

Survival data were finally updated in March 2006, 2 years after accrual of the last patient. Figure 1 shows PFS and OS curves of the 27 eligible patients. Median PFS was 0.79 years (95% confidence interval, 0.52–1.40 years) and PFS at 1 and 2 years was 37 and 15%, respectively. Median OS was 6.1 years and OS at 2 and 5 years was 89 and 65%, respectively.

Overall survival was longer for stage-IVa patients than for stage-IVb patients (Figure 2, median, 6.8 years and 3.5 years, respectively), but PFS was similar (Figure 3, median, 0.79 years for IVa patients and 0.78 years for IVb patients).

Pattern of relapse

As of the data cut-off, 26 of the 27 eligible patients had experienced tumour relapse. Sites of initial relapse comprised the primary site only in seven cases (27%), pleural or pericardial dissemination in seven cases (27%) and primary site and pleural/pericardial dissemination in nine cases (35%). Thus, 23 of the 26 patients with relapse initially showed regrowth of the primary and/or pleural or pericardial dissemination, with only three patients (12%) showing initial relapse at distant organs.

DISCUSSION

Few prospective trials of chemotherapy have been described for patients with advanced thymoma. Most prior studies have combined stage-III, localised disease and stage-IV, disseminated disease (Table 3). In addition, most have also included both thymoma and thymic carcinoma histology.

We have reported results for patients with stage-IV disease, for which systemic therapy should be the first choice. Among previous studies, only those from the ECOG separately reported results for stage-III and stage-IV patients (Loehrer *et al*, 1994, 1997). The ECOG took 9 years to accrue 31 patients with stage-IV disease, including patients with thymic carcinoma (Loehrer *et al*, 1994). We prospectively accrued patients with thymoma only and excluded thymic carcinoma, as thymoma and thymic carcinoma clearly differ in clinical presentation and prognosis, and trials involving these pathologies should, thus, be reported separately (Eng *et al*, 2004; Giaccone, 2005; Lemma *et al*, 2008).

Trials of systemic chemotherapy for thymoma have reported response rates of 50–90%, so this tumour is generally considered sensitive to chemotherapy (Thomas *et al*, 1999). Dose-dense chemotherapy such as the CODE four-drug combination has been argued to be theoretically suitable for the treatment of such chemosensitive tumours (Murray, 1987).

Although our results showed that dose-dense CODE chemotherapy could be safely administered to thymoma patients, efficacy was not remarkable. The overall response rate was about 60%, no different from prior reports employing conventional-dose chemotherapy (Table 3). Progression-free survival was 9 months, falling far short of the expected 2 years. Although OS studies compared favourably with the corresponding ECOG trial (Loehrer *et al*, 1994), attempting to reach a valid conclusion would be difficult due to the small sample sizes. In addition, OS could be

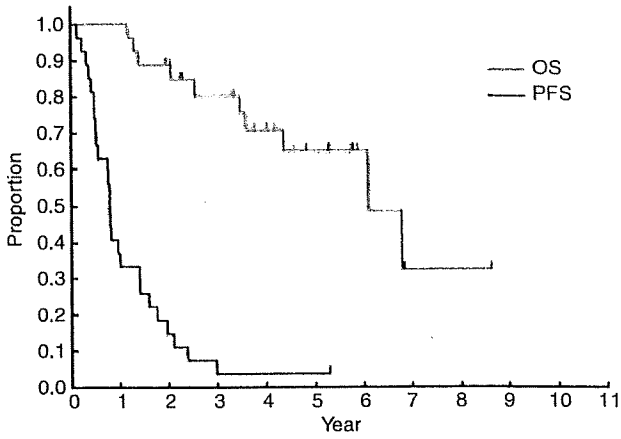

Figure 1 Progression-free survival and OS of the 27 eligible patients.

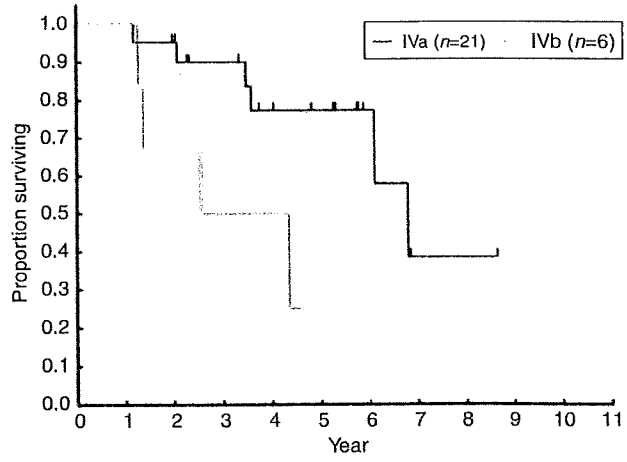

Figure 2 Overall survival according to Masaoka stage (stage IVa *vs* IVb).

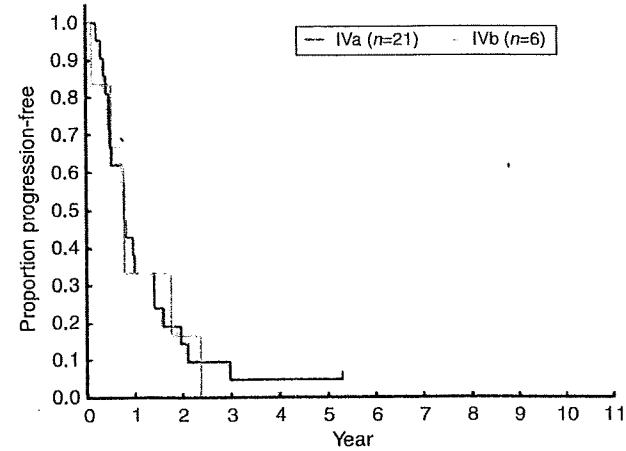

Figure 3 Progression-free survival according to Masaoka stage (stage IVa *vs* IVb).

Table 3 Reports of combination chemotherapy for thymoma

Regimen	Stage	Patients[a]	ORR	Reference
Anthracycline-containing regimens				
ADOC (S)	III/IV	32	91%	Fornasiero et al (1990)
PAC (G)	IV	30	50%	Loehrer et al (1994)
PAC (G)	III	23	70%	Loehrer et al (1997)
ADOC (S)	III/IV	16	81%	Berruti et al (1999)
PAC (G)	III/IV	22	77%	Kim et al (2004)
PAE (S)	III/IV	30	73%	Lucchi et al (2006)
CAMP (S)	III/IV	14	93%	Yokoi et al (2007)
CODE (G)	IV	27	59%	Current study
Non-anthracycline-containing regimens				
PE (G)	III/IV	16	56%	Giaccone et al (1996)
VIP (G)	III/IV	20	35%	Loehrer et al (1997)
CP (G)	III/IV	23	35%	Lemma et al (2008)

Abbreviations: ADOC = doxorubicin, cisplatin, vincristine, cyclophosphamide; CAMP = cisplatin, doxorubicin, methylpredonisolone; CODE = cisplatin, vincristine, doxorubicin, etoposide; CP = carboplatin, paclitaxel; G = prospective multicenter group trial; ORR = overall response rate; PAC = cisplatin, doxorubicin, cyclophosphamide; PAE = cisplatin, epidoxorubicin, etoposide; PE = cisplatin, etoposide; S = single-center experience; VIP = etoposide, ifosfamide, cisplatin. [a]Number of assessable patients.

greatly affected by post-study local therapy especially in patients with stage-IVa disease, as combined therapy trial including stage-IVa patients suggested (Kim *et al*, 2004). In fact, this might be one reason why OS of stage-IVa patients was much longer than that of stage-IVb patients, whereas PFS was similar.

It could be argued that shortened CODE chemotherapy, used in Japan due to feasibility problem, led to inadequate results due to insufficient total dosages of chemotherapy drugs. However, another intensive chemotherapy, ETP-IFX-CDDP (VIP) supported by G-CSF, has also reported disappointingly low response rates and no better survival (Loehrer *et al*, 2001). Hanna *et al* (2001) reported five patients with prior chemotherapy treated with high-dose chemotherapy and stem cell support, but concluded that no superiority to conventional therapy was evident. Taken together with our results, intensification of chemotherapy does not appear sufficiently promising for treating advanced thymoma.

Many prior chemotherapy studies have included platinum and anthracyclines in their regimens. Non-anthracycline approaches contained regimens such as VIP (Loehrer *et al*, 2001), ETP-CDDP (Giaccone *et al*, 1996) and paclitaxel-carboplatin (Lemma *et al*, 2008) tended to yield lower response rates of 32-56% as compared with regimens including anthracycline (Table 3). It might, thus, be suggested that both anthracycline and platinum should, thus, be included in thymoma chemotherapy, at least in current clinical practice.

Favourable results have recently been reported with multimodality therapy, including surgical resection of stage-IVa disease (Kim *et al*, 2004; Yokoi *et al*, 2007). In fact, about two-thirds of eligible patients in our trial received local therapy after chemotherapy, including surgery in eight patients. This could have affected the outcome of the patients, as discussed above. However, small sample size and patient selection preclude reaching any definitive conclusion. When and what local therapy, if any, would benefit patients with disseminated thymoma, remains yet to be established. Further studies are warranted.

The present study shows several additional limitations. One is that we did not perform a central review of histology, and, thus, could not provide WHO classifications of histology (Okumura *et al*, 2002; Travis *et al*, 2004). This makes comparisons with results from other reports difficult. Central pathology review and preferably tissue collection would be very important in future trials.

In addition, due to the shorter-than-expected PFS, the planned CT scan interval of every 6 months might not have accurately evaluated PFS (Freidlin *et al*, 2007). Future trials might require more frequent scans.

In conclusion, we have reported that weekly dose-dense chemotherapy can be safely administered to patients with thymoma. However, efficacy seems similar to that in patients treated with conventional doses. More research on optimal systemic therapy and the role of local modalities would appear to be necessary.

Clinical Studies

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