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.

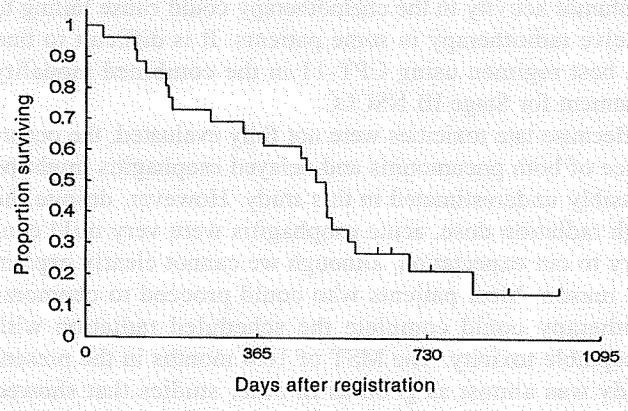

Figure 1. The overall survival curve of all patients enrolled in the study.

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 INVESTIGATION

THE IMPACT OF RADIATION DOSE AND FRACTIONATION ON OUTCOMES FOR LIMITED-STAGE SMALL-CELL LUNG CANCER

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Purpose: To review the treatment outcomes of limited-stage small-cell lung cancer (LS-SCLC) patients and to compare the outcomes among three groups in which the total radiation doses were 45 Gy with accelerated hyperfractionation (AHF), <54 Gy with standard fractionation (SF), and ≥54 Gy with SF.

Methods and Materials: LS-SCLC patients that had been treated with chemoradiotherapy between 1997 and 2007 at Aichi Cancer Center Hospital were reviewed in this study. Of the 127 eligible patients, there were 37 patients in the AHF group, 29 in the SF <54 Gy group, and 61 in the SF ≥54 Gy group.

Results: Fifty-five patients (43%) were alive at the time of this analysis, and the median follow-up time of the surviving patients was 33 months. The median survival times were 30.0 months (95% confidence interval [CI] 16.3–43.7) for the AHF group, 14.0 months (CI 6.6–21.4) for the SF <54 Gy group, and 41.0 months (CI 33.9–48.1) for the SF ≥ 54 Gy group. As for the local control rates, and the overall and progression-free survival rates, all outcomes were significantly lower in the SF <54 Gy group than in the other two groups, although no significant difference was found between the AHF and SF ≥54 Gy groups.

Conclusions: These results suggest the importance of a high dose of radiation when using once-daily regimen. This study will support future prospective studies to establish optimal radiation doses and fractionation. © 2009 Elsevier Inc.

Small-cell lung cancer, Radiation therapy, Radiation dose, Fractionation, Accelerated hyperfractionation.

INTRODUCTION

Chemoradiotherapy is currently the standard treatment for limited-stage small-cell lung cancer (LS-SCLC) (1). Although thoracic radiotherapy (TRT) has been established as an integral component of the treatment platform for LS-SCLC, some questions regarding the optimal radiotherapy approach have also arisen. With regard to fractionation, Turrisi *et al.* determined that accelerated hyperfractionation (AHF) is superior to standard fractionation (SF) in an Intergroup Phase III study (2). However, despite the significant improvement in long-term survival, a pattern of care study found that only 10% of patients with LS-SCLC received a twice-daily regimen because of the inconvenience of twice-daily treatment sessions and the increased rate of severe esophageal toxicity seen with this regimen, whereas more than 80% received once-daily TRT (3). Although traditionally modest doses of TRT (45–50 Gy) are often used in once-daily 1.8- to 2-Gy fractions (4, 5), the optimal total dose for a once-daily regimen has not been proven. In addition, it is also still unclear whether twice-daily TRT of 45 Gy in 3 weeks is superior to a higher total dose than traditional modest doses delivered with a once-daily regimen. In this study, we reviewed the treatment outcomes of LS-SCLC patients that were treated with chemoradiotherapy at Aichi Cancer Center Hospital and compared the outcomes among three groups in which the total radiation doses were 45 Gy with a twice-daily regimen, less than 54 Gy with a once-daily regimen, and equal or greater than 54 Gy with a once-daily regimen.

METHODS AND MATERIALS

Patient selection

LS-SCLC patients that had been treated with chemoradiotherapy between 1997 and 2007 at Aichi Cancer Center Hospital and who met the eligibility criteria were enrolled into this retrospective study. The diagnosis of SCLC was confirmed by histologic or cytologic findings in all cases. Limited-stage was defined as disease confined to one hemithorax with or without bilateral supraclavicular node metastasis. The eligibility criteria consisted of no previous treatment and an Eastern Cooperative Oncology Group performance status

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of 0–2. Additional eligibility criteria were as follows: they had not undergone surgery for LS-SCLC nor had been treated with a radiation field, not including elective nodal irradiation, because the significance of omitting elective nodal irradiation remains unclear (6). Written informed consent was obtained from all patients before treatment. Each patient underwent the following studies: chest radiography and fiberoptic bronchoscopy, complete blood count and biochemical tests, a computed tomography (CT) scan of the thorax and abdomen, a CT scan or magnetic resonance imaging of the brain, and a radionuclide bone scan, or positron emission tomography. Positron emission tomography was used for a few patients (7%) who were treated after 2001 according to the physician's preference. Bone marrow aspiration or biopsy was performed in cases of neutropenia and thrombocytopenia.

Radiation therapy technique

TRT was carried out with linear accelerators, and the energy of 6–10 MV photons was used. The TRT fields were changed from anteroposterior-posteroanterior fields to parallel opposed oblique fields after 30 Gy in the twice-daily regimen and 36–40 Gy in the once-daily regimen. Most patients (83%) that were eligible for this study were treated using conventional fluoroscopic simulation techniques at the start of the TRT, and CT simulation techniques were used only for the planning of the boost fields. The other 17% were treated using CT simulation techniques throughout the entire TRT. The other planning techniques were similar to those in our previous report on non–small-cell lung cancer (7). TRT was administered twice daily (1.5 Gy per fraction, with a 6 h or more interval between fractions) for a total dose of 45 Gy in 3 weeks or once-daily (1.8–2.0 Gy per fraction) for a total dose of 39.6–66 Gy in 4–7 weeks. After the TRT, prophylactic cranial irradiation (PCI) was administered to the patients who had a complete or near-complete response (10). The PCI consisted of 24 Gy in 2 Gy per fractions or 25 Gy in 2.5 Gy per fractions once daily, 5 days per week.

All patients who entered the clinical trial were treated with the AHF regimen. However, there were no adequate rationale for a decision about a patient's TRT dose and fractionation. The TRT dose and fractionation was decided according to the physician's preference.

Chemotherapy

In principle, the patients were treated with four cycles of chemotherapy and received at least one cycle of chemotherapy concurrent with TRT. The chemotherapy was given in a 28-day cycle in the concurrent phase and a 21-day cycle in the sequential phase. The most commonly used regimens were cisplatin/etoposide, carboplatinum/etoposide, and cisplatin/irinotecan. As a general rule, the cisplatin/etoposide regimen consisted of cisplatin (80 mg/m^2 intravenously) on day 1 and etoposide (100 mg/m^2 intravenously) on Days 1, 2, and 3. The carboplatinum/etoposide regimen consisted of carboplatinum (area under the blood concentration-time curve: 5 intravenously) on Day 1 and etoposide (100 mg/m^2 intravenously) on Days 1, 2, and 3. The cisplatin/irinotecan regimen was only performed sequentially with TRT and consisted of cisplatin (80 mg/m^2 intravenously) on Day 1 and irinotecan (60 mg/m^2 intravenously) on Days 1, 8, and 15.

Study design and statistical analysis

All available radiation records and charts were reviewed to assess patient and tumor characteristics and the details of treatment and outcome. Tumor response was classified in accordance with the Response Evaluation Criteria in Solid Tumors criteria (9). Complications were graded in accordance with the National Cancer Institute's Common Toxicity Criteria, version 3.0 (10). The date of the last follow-up was defined as the last recorded information available for the patient. Only 3 patients were lost to follow-up. Survival was measured from the start date of any treatment to the date of the last follow-up or death from any cause. Local failure, defined as locoregional progression on CT (including the primary tumor and the bilateral mediastinal and ipsilateral hilar lymph nodes), was measured from the start date of any treatment to the date of the first evidence of locoregional disease progression. Concurrent local and distant failures were scored as local failures for the first failure sites. Progression-free survival was measured from the start date of any treatment until the date of local or distant failure.

Overall survival (OS), overall local, and overall progression-free survival were calculated using Kaplan-Meier estimates. Subgroup analysis was used to compare the outcomes among the three groups, in which the total radiation doses were 45 Gy with AHF, <54 Gy with SF, and ≥54 Gy with SF, using the log–rank test. Moreover, sex, age at diagnosis, performance status, disease stage (I, II, vs. III), PCI (yes vs. no), total chemotherapy cycles (<3 vs. ≥3), concurrent chemotherapy (yes vs. no), and the duration of TRT (<40 days vs. ≥40 days) were also assessed for their impact on OS using the log–rank test. Fisher's exact test was used for comparisons of categorical data. Cox's proportional hazards model was used for multivariate analysis. $p < 0.05$ was considered significant.

RESULTS

Patient and treatment characteristics

A total of 127 patients were enrolled into the study. The median total dose of TRT with the once-daily regimen was 54 Gy; therefore, we divided the patients that had been treated with the once-daily regimen into two groups using the median total dose of 54 Gy for the subgroup analysis. The characteristics of the 127 eligible patients are shown in Table 1. Fifteen patients (40%) from the AHF group entered a clinical trial, but no patients from the other two groups did. The baseline characteristics were balanced in terms of sex, performance status, stage, and chemotherapy cycles. However, there was a slight imbalance in age; the patients in the AHF group tended to be younger than those in the other two groups, and the rate of patients older than age 75 years was lower than in the other two groups, but these differences were not significant ($p = 0.15$). There were significant differences in the rate of patients that received concurrent chemotherapy and PCI among the three groups ($p = 0.012$, $p < 0.001$, respectively). Fifty-five (43%) patients were alive at the time of this analysis, and the median follow-up time of the surviving patients was 33 months (range, 2–118 months). The median follow-up time of the surviving patients was 34 months (range, 16–96 months) for the AHF group, 67 months (range, 12–91 months) for the SF <54 Gy group, and 22 months (range, 2–118 months) for the SF ≥54 Gy group. There were no significant differences in the median follow-up time of the surviving patients among the three groups ($p = 0.32$).

As a result, 84% received four or more cycles of chemotherapy. Eight percent received three cycles, and 8% received less than two cycles either because the patient refused continuation

Table 1. Patient and tumor pretreatment characteristics

Characteristic	Prescription group			p value*
	AHF group (n = 37)	SF <54 Gy group (n = 29)	SF ≥54 Gy group (n = 61)	
Age (y)	58 (40–68)	70 (51–82)	66 (29–81)	
≥75 (%)	0 (0%)	3 (10%)	5 (8%)	0.15
Sex (%)				0.59
Male	30 (81%)	25 (86%)	54 (82%)	
Female	7 (19%)	4 (14%)	7 (18%)	
Performance status				0.29
0	13 (35%)	7 (25%)	20 (33%)	
1	24 (65%)	20 (68%)	36 (59%)	
2	0 (0%)	2 (7%)	5 (8%)	
Stage				0.20
I	0 (0%)	1 (3%)	6 (10%)	
II	4 (11%)	0 (0%)	4 (7%)	
IIIA	22 (59%)	11 (38%)	24 (39%)	
IIIB	11 (30%)	17 (59%)	27 (44%)	
CHT cycles	3.9 (2–5)	3.7 (1–6)	3.9 (1–6)	0.72
≥3 cycles	33 (89%)	27 (93%)	56 (92%)	
Concurrent CHT	37 (100%)	23 (79%)	56 (92%)	0.012*
Total dose (Gy)	45 (45)	50 (39.6–52.2)	56 (54–63)	<0.001*
Duration of TRT (days)	21 (19–27)	41 (30–56)	43 (36–59)	<0.001*
PCI	24 (65%)	6 (21%)	18 (30%)	< 0.001*

Abbreviations: AHF = accelerated hyperfractionation; SF = standard fractionation; CHT = chemotherapy; TRT = thoracic radiotherapy; PCI = prophylactic cranial irradiation.

Age and total dose data are presented as the median value. CHT cycles data are presented as the mean value. The numbers in square brackets indicate the range of age and CHT cycles.

* Fisher's exact test.

of the chemotherapy or their leukocyte or platelet counts or renal function did not return to levels at which chemotherapy could be performed. Most patients (91%) received at least one cycle of concurrent chemotherapy with TRT, whereas the remaining 9% only received sequential chemotherapy because the radiation field sizes of these patients were too large as the primary tumor was located in the inferior lobe or the primary tumor was so bulky that concurrent chemoradiotherapy was considered to carry a high risk of severe radiation pneumonitis (11). All patients received at least one cycle of platinum-based agents/etoposide regimen regardless of the TRT regimen. The cisplatin/irinotecan regimen was only performed sequentially with TRT for 24% of patients in the AHF group and 16% of the SF ≥54 Gy group.

Tumor response

Table 2 shows the tumor response in each group. The overall response rate was 94% (95% confidence interval [CI] 91–98%, 58% complete response rate [CI 50–67%], and 36% partial response rate [CI 28–45%]) for all eligible patients. There was a significantly lower rate of complete response in the SF <54 Gy group than in the AHF and SF ≥54 Gy groups (p = 0.018 and 0.0062, respectively). There was a significantly higher rate of complete response in the AHF group than in the SF ≥54 Gy group (p = 0.042).

Table 2. Tumor response in each group

Response	Prescription group						p value*
	AHF (n = 37)		SF <54 Gy (n = 29)		SF ≥54 Gy (n = 61)		
	No.	%	No.	%	No.	%	
Overall response	34	92%	27	93%	59	97%	0.32
CR	27	73%	11	38%	36	59%	0.02*
PR	7	19%	16	55%	23	38%	
SD	0	0%	1	3%	2	3%	
PD	3	8%	1	3%	0	0%	

Abbreviations: AHF = accelerated hyperfractionation; SF = standard fractionation; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

* Fisher's exact test.

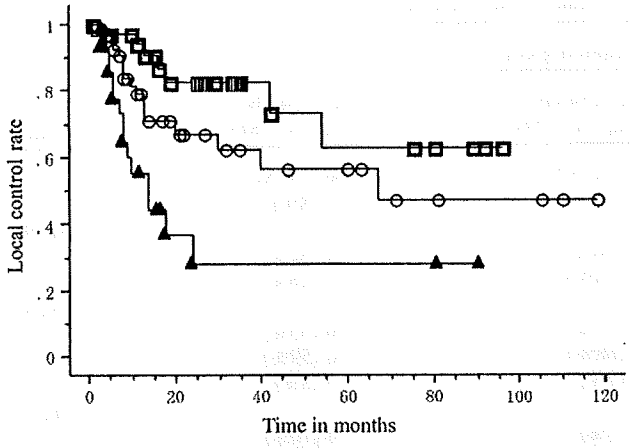

Fig. 1. The local control rates for patients with a total dose of 45 Gy with accelerated hyperfractionation (□), <54 Gy with standard fractionation (▲), and ≥54 Gy with standard fractionation (○).

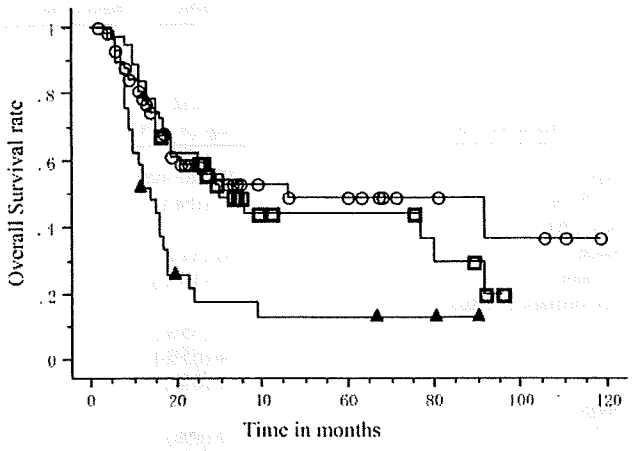

Fig. 2. Overall survival for patients with a total dose of 45 Gy with accelerated hyperfractionation (□), <54 Gy with standard fractionation (▲), and ≥54 Gy with standard fractionation (○).

Local control and progression-free survival

Figure 1 shows the local control rates for each group. The 3-year local control rates were 61.1% (CI 50.3–71.9%) for all eligible patients, 81.3% (CI 67.2–95.5%) for the AHF group, 27.7% (CI 5.0–50.4%) for the SF <54 Gy group, and 61.2% (CI 44.8–77.6%) for the SF ≥54 Gy group. The local control rate was also significantly lower for the SF <54 Gy group than the AHF and SF ≥54 Gy groups (p = 0.0016 and 0.011, respectively). Local control for the AHF group tended to be superior to that for the SF ≥54 Gy group, although no statistically significant difference was found (p = 0.096).

The 3-year progression-free survival rates were 28.1% (CI 19.5–36.7%) for all eligible patients, 37.5% (CI 21.5–53.5%) for the AHF group, 7.5% (CI 0–17.5%) for the SF <54 Gy group, and 33.2% (CI 19.7–46.7%) for the SF ≥54 Gy group. Progression-free survival was also significantly lower for the SF <54 Gy group than for the AHF and SF ≥54 Gy groups (p = 0.015 and 0.013, respectively). Progression-free survival was similar in the AHF group and the SF ≥54 Gy group (p = 0.80).

Overall survival

Figure 2 shows the survival curves for each group. The median survival time of all eligible patients was 24.0 months (CI 18.1–29.9 months). The median survival times were 30.0 months (CI 16.3–43.7 months) for the AHF group, 14.0 months (CI 6.6–21.4 months) for the SF <54 Gy group, and 41.0 months (CI 33.9–48.1 months) for the SF ≥54 Gy group. The 3-year survival rates were 41.2% (CI 31.6–50.8%) for all eligible patients, 44.1% (CI 26.5–61.7%) for the AHF group, 13.8% (CI 0–27.3%) for the SF <54 Gy group and 53.1% (CI 38.6–67.6%) for the SF ≥54 Gy group. There was a significantly lower rate of OS in the SF <54 Gy group than in the AHF and SF ≥54 Gy groups (p = 0.0018 and 0.00036, respectively). OS for the SF ≥54 Gy group seemed to be slightly superior to that for the AHF group, although no statistically significant difference was found (p = 0.64).

Factors associated with overall survival

Table 3 shows the effects of patient characteristics, disease factors, and treatment parameters on OS according to univariate analysis. To evaluate further the independent effects of disease stage, chemotherapy cycles, concurrent chemotherapy, PCI,

Table 3. Factors associated with overall survival according to univariate analysis

Factors	No. of patients	3-year OS (95% CI)	p value
Sex			0.367
Male	109	40.8% (33.1–48.5)	
Female	18	41.8% (36.1–47.5)	
Age (y)			0.652
<75	119	40.6% (33.2–48.0)	
≥75	8	48.6% (43.6–53.6)	
PS			0.546
0, 1	120	42.0% (34.6–49.4)	
2	7	28.6% (23.6–33.6)	
Stage			0.016*
I, II	15	80.0% (78.3–81.7)	
III	112	35.7% (28.3–43.1)	
CHT cycle			0.033*
<3	11	43.4% (35.8–51.0)	
≥3	116	20.0% (14.2–25.8)	
Concurrent CHT			0.026*
Yes	116	43.7% (36.1–51.3)	
No	11	20.0% (17.3–22.7)	
Treatment group			<0.001*
AHF	37	44.1% (26.5–61.7)	
SF ≥54 Gy	29	53.1% (38.6–67.6)	
SF <54 Gy	61	13.8% (0–27.3)	
Duration of RT (days)			0.821
<40	66	41.3% (31.0–51.6)	
≥40	61	40.0% (29.8–50.2)	
PCI			0.089
Yes	48	48.1% (36.6–59.6)	
No	79	35.6% (31.6–39.6)	

Abbreviations: CI = confidence interval; PS = performance status; CHT = chemotherapy; NA = not applicable; AHF = accelerated hyperfractionation; SF = standard fractionation; RT = radiation therapy; PCI = prophylactic cranial irradiation.

* Statistically significant.

Table 4. Factors associated with overall survival according to multivariate analysis

Factors	Hazard ratio of death (95% CI)	*p* value
Stage (I, II vs. III)	0.24 (0.074–0.78)	0.017*
CHT cycle (<3 vs. ≥3)	0.50 (0.24–1.07)	0.073
Concurrent CHT (yes vs. no)	0.61 (0.29–1.31)	0.20
Treatment group (AHF vs. SF ≥54 Gy SF 54 Gy)	NA	0.033*
PCI (yes vs. no)	0.75 (0.43–1.31)	0.31

Abbreviations: CHT = chemotherapy; NA = not applicable; AHF = accelerated hyperfractionation; SF = standard fractionation.
* Statistically significant.

and treatment group on OS, a multivariate Cox proportional hazards regression analysis was performed. This analysis included those factors that had displayed a p value <0.10 in the univariate analysis. As a consequence, disease stage and treatment group remained significant factors in the multivariate analysis (Table 4).

Toxicity

Documentation concerning toxicity data was not available for 6 patients (2 in each group), which left 121 patients assessable for toxicity. Only late toxicity ≥Grade 2 was assessed from the available information of each chart. There were only 2 treatment-related deaths (one in the SF <54 Gy group and the other in the SF ≥54 Gy group). Both patients died of radiation pneumonitis. Five patients developed Grade 2 radiation pneumonitis, 4 in the SF <54 Gy group and 1 in the SF ≥54 Gy group. Apart from the toxicities described, no other information about late toxicity was noted in the charts.

DISCUSSION

In our study, the comparison of overall, progression-free, and local control survival rates and the rate of complete response suggested that TRT administered with a total dose of <54 Gy by once-daily regimen was more disadvantageous than TRT treated with a total dose of ≥54 Gy in a once-daily regimen or a total dose of 45 Gy administered using the AHF regimen, and the difference was statistically significant for all outcomes. These results clearly demonstrate that radiation intensification improves the complete response rate and local control and that improved local control translates into improved OS. Furthermore, these results also suggest the importance of a high dose of radiation when using a once-daily regimen.

Because SCLC has high radiation sensitivity (12), recent pattern of care studies have shown that the traditional modest doses of TRT that are used in once-daily 1.8- to 2-Gy fractions are also widely used for LS-SCLC in Japan and Turkey (4, 5). However, although response rates are high, local control rates have been poor in this TRT setting. Intensifying the radiotherapy effect by accelerating its delivery was one of the initial strategies explored in prospective trials. Turrisi *et al.* (2) randomly assigned 471 LS-SCLC patients to either 45 Gy in 5 weeks (1.8 Gy once-daily for 25 fractions) or 45 Gy in 3 weeks (1.5 Gy twice-daily for 30 fractions) beginning with the first of four cycles of PE. The 5-year survival rate was 26% with accelerated TRT compared with 16% for the conventional TRT ($p = 0.04$), and the accelerated TRT arm was also superior to conventional TRT in local tumor control ($p = 0.06$). These data strongly suggest that attempts designed at improving local tumor control can favorably impact on the long-term outcome of patients with LS-SCLC. However, despite the significant improvement in long-term survival, only 10% of patients with LS-SCLC received a twice-daily regimen (3). Moreover, a second trial performed by the North Central Cancer Treatment Group reported negative results with a twice-daily regimen, although overall treatment times and total radiation doses were identical in each arm of the North Central Cancer Treatment Group trial (13). Therefore, different strategies were considered that might increase the local control rate with chemoradiotherapy. Accelerated fractionation via the concomitant boost technique uses once-daily irradiation early in the course of treatment and then twice-daily irradiation toward the end. Komaki *et al.* (14) reported a Phase 1 study (Radiation Therapy Oncology Group 97-12) using this regimen to improve local control by increasing the dose of TRT given with concurrent cisplatin/etoposide without causing acute severe esophagitis. They found that 61.2 Gy was the maximum tolerated dose, and there was a suggestion of improvement in the estimated short-term survival rate (18 months) by dose escalation from 50.4 Gy to 61.2 Gy (25% and 82%, respectively). Roof *et al.* (15) also showed a clear dose–response curve between 54 and 63 Gy with a once-daily regimen, although they did not find a significant difference in outcome because of their small sample size of 54 patients.

Obviously, there are problems that limit the interpretation of a single institutional retrospective review. We recognize the imbalance among our three groups. The rates of patients receiving PCI and concurrent chemotherapy were significantly different among the three groups (Table 1), although the multivariate analysis proved that these factors were not associated with OS. Another difficulty associated with retrospective reviews is the accurate assessment of toxicity. The rate of Grade 2-4 toxicities in our study was lower than those reported elsewhere. Although the patient charts were thoroughly scrutinized, the documentation concerning complications may not have been as thorough as it would have been in a prospective trial.

Whether twice-daily TRT to 45 Gy in 3 weeks is superior to a higher total dose than traditional modest doses delivered with a once-daily regimen is still unclear. Our results did not find a significant difference in outcome between the AHF group with a total dose of 45 Gy and the SF group with a total dose of ≥54 Gy. However, there was a significantly higher

rate of complete response in the AHF group compared with the SF ≥54 Gy group ($p = 0.042$), and the local control for the AHF group tended to be superior to that for the SF ≥54 Gy group. These results indicate that in the once-daily regimen much more than 54 Gy is necessary to achieve local control at the same level as 45 Gy with the AHF regimen. Despite the significantly higher rate of complete response and local control in the AHF group compared with the SF ≥ 54 Gy group, progression-free survival and OS were similar between the AHF group and the SF ≥54 Gy group ($p = 0.80$ and 0.64, respectively). We think that the reason was our small sample size. On the other hand, these data indicated that patients in the AHF group died from systemic disease as did those in the SF ≥54 Gy group, despite the better local control in the AHF group compared with the SF ≥54 Gy group. Therefore, another chemotherapy strategy such as integrating newer chemotherapy agents (16) or dose-intense regimens using either growth factors or stem-cell support (17) may be necessary for the platform of the curative approach to LS-SCLC.

Further intensification of TRT regimens such as a Phase III trial is under development by the Cancer and Leukemia Group B and the Radiation Therapy Oncology Group (18). This randomized trial is designed to compare three TRT approaches with four cycles of PE, with the three regimens being 45 Gy in 3 weeks (1.5 Gy twice-daily for 30 fractions), 70 Gy in 7 weeks (2.0 Gy once-daily for 35 fractions), and 61.2 Gy in 5 weeks (1.8 Gy accelerated fractionation via concomitant boost). We think that this trial will demonstrate the optimal method of radiation dose intensification. However, at this time, 45 Gy twice-daily TRT should be considered as the standard treatment for LS-SCLC because there are no Phase III once-daily trials that have shown better outcomes than the twice-daily regimen.

In conclusion, this analysis suggests that disease stage and treatment groups that are stratified according to 45 Gy with AHF, <54 Gy with SF, and ≥54 Gy with SF are independent factors associated with improved OS in patients with LS-SCLC and the potential importance of a high dose of radiation when using a once-daily regimen. However, there are problems that limit the interpretation of our single institutional retrospective review. There were some prognostic differences in the three groups compared, especially in the rates of patients receiving PCI and concurrent chemotherapy. A future prospective study of TRT regimens in the setting of chemoradiotherapy for LS-SCLC is needed to establish optimal radiation doses and fractionation, and such a study is under development by the Cancer and Leukemia Group B and Radiation Therapy Oncology Group.

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

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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).

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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

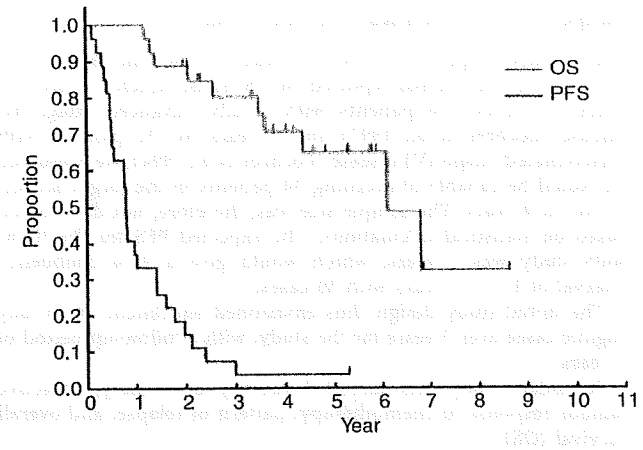

Figure 1 Progression-free survival and OS of the 27 eligible patients.

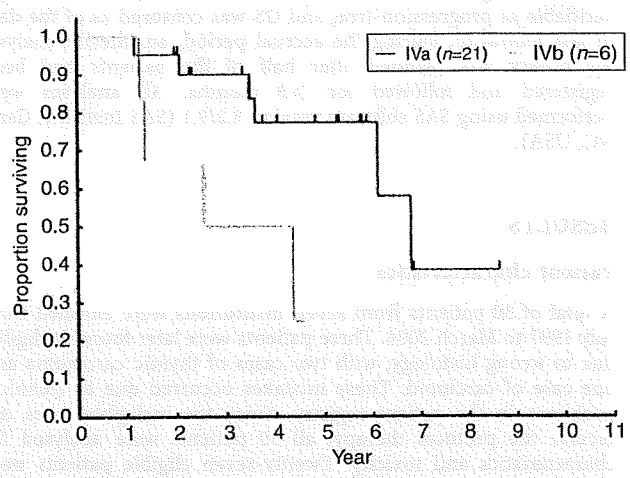

Figure 2 Overall survival according to Masaoka stage (stage IVa *vs* IVb).

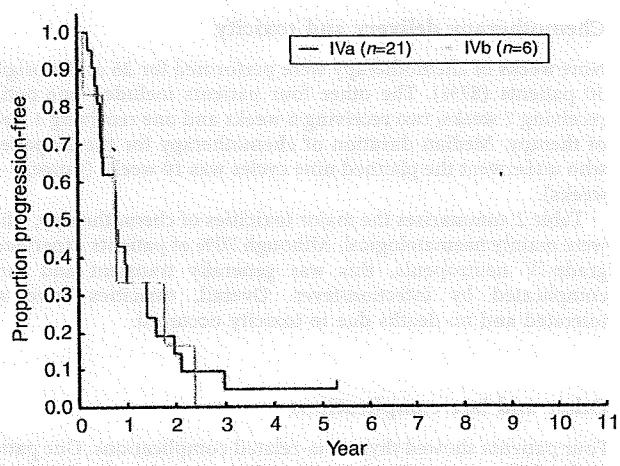

Figure 3 Progression-free survival according to Masaoka stage (stage IVa *vs* IVb).

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

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 multi-modality 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.

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Appendix 1

STUDY PARTICIPANTS

The following institutions and investigators participated in the trial:

Asahikawa Medical College (Yoshinobu Osaki), National Cancer Center Hospital East (Yutaka Nishiwaki, Kaoru Kubota, Nagahiro Saijo), National Cancer Center Hospital (Tomohide Tamura, Noboru Yamamoto, Hideo Kunitoh), Kanagawa Cancer Center (Kazumasa Noda, Fumihiro Oshita), Niigata Cancer Center Hospital (Akira Yokoyama, Yuko Tsukada), Kinki University Hospital (Kazuhiko Nakagawa, Isamu Okamoto) and Osaka City General Hospital (Koji Takeda, Haruko Daga).

Appendix 2

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Original Article

Cisplatin and Etoposide Chemotherapy Combined with Early Concurrent Twice-daily Thoracic Radiotherapy for Limited-disease Small Cell Lung Cancer in Elderly Patients

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Objective: The optimal management of elderly patients with limited-disease small cell lung cancer (LD-SCLC) has not been established.
Methods: The records of elderly (≥70 years of age) patients with LD-SCLC who had been treated with etoposide and cisplatin chemotherapy with early concurrent twice-daily thoracic radiotherapy (TRT) were reviewed retrospectively.
Results: Of the 25 elderly patients with LD-SCLC identified, 12 (48%) individuals received etoposide–cisplatin chemotherapy with early concurrent twice-daily TRT. The main toxicities of this treatment regimen were hematologic, with neutropenia of Grade 4 being observed in all patients and febrile neutropenia of Grade 3 in eight patients during the first cycle of chemoradiotherapy. The toxicity of TRT was acceptable, with all patients completing the planned radiotherapy within a median of 29 days (range, 19–33). No treatment-related deaths were observed. The median progression-free survival and overall survival times were 14.2 months (95% confidence interval, 4.3–18.2) and 24.1 months (95% confidence interval, 11.3–27.2), respectively.
Conclusions: Etoposide–cisplatin chemotherapy with early concurrent twice-daily TRT was highly myelotoxic in elderly patients with LD-SCLC, although no treatment-related deaths were observed in our cohort. Prospective studies are required to establish the optimal schedule and dose of chemotherapy and TRT in such patients.

Key words: elderly – small cell lung cancer – chemoradiotherapy – cisplatin – etoposide – concurrent thoracic radiotherapy

INTRODUCTION

Small cell lung cancer (SCLC) accounts for 10–15% of all lung cancer cases, with individuals aged 70 years or older constituting up to 25–40% of the SCLC patients (1,2). Limited-disease (LD) SCLC is a disease that is confined to one hemithorax and its regional lymph nodes and which can be encompassed by a single radiation therapy port. About 30–40% of all SCLC patients present with LD-SCLC (1,2). The proportion of elderly SCLC patients continues to increase with the growing geriatric population (1,3).

The combination of radiotherapy and chemotherapy, specifically etoposide and cisplatin chemotherapy with early concurrent twice-daily thoracic radiotherapy (TRT), is now regarded as the standard treatment for LD-SCLC (4). However, many clinical trials of potential new treatments for LD-SCLC have excluded elderly patients for various reasons, such as the presence of concomitant chronic illness,

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a decline in organ function that may interfere with drug clearance and possible decreased bone marrow tolerance to myelosuppressive agents (5). The optimal management of elderly patients with LD-SCLC has therefore not been defined to date.

We have now performed a retrospective analysis to evaluate patient characteristics as well as treatment delivery, toxicity and antitumor efficacy for elderly individuals (70 years or older) with LD-SCLC who were treated with etoposide and cisplatin chemotherapy and early concurrent twice-daily TRT.

PATIENTS AND METHODS

We retrospectively evaluated the records of elderly ($\geq$70 years) patients with LD-SCLC who were treated at Kinki University School of Medicine from January 2003 to December 2008. All patients had a pathological diagnosis of SCLC. LD-SCLC was defined as cancer that is confined to one hemithorax including contralateral mediastinal and hilar lymph nodes as well as ipsilateral or bilateral supraclavicular lymph nodes, but excluding malignant pleural effusion. Response evaluation was assessed after completion of treatment on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST). Laboratory testing and toxicities were graded weekly during the whole treatment according to the National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3). Progression-free survival time was measured from the date of initiation of treatment to the date of disease progression. Overall survival time was measured from the date of initiation of treatment to death or to the time that the patient was last known to be alive. After completion of all treatment, patients were followed up at 1- to 2-month intervals until the time of progression or death. Median progression-free survival time and overall survival time were estimated by the Kaplan–Meier method.

RESULTS

Patient Characteristics

Of the 170 SCLC patients treated between 2003 and 2008, 48 individuals were diagnosed with LD-SCLC and 25 of these individuals were 70 years of age or older. Among these 25 patients, 12 (48%) elderly patients with LD-SCLC received etoposide and cisplatin chemotherapy with early concurrent twice-daily TRT. The characteristics of these 12 patients are shown in Table 1. They included eight men and four women as well as seven individuals aged between 70 and 74 years and five aged 75 years or older. All the patients were in good general condition, although they had some complications. The remaining 13 patients' characteristics are shown in Table 2. Two of the 13 elderly patients with LD-SCLC were treated with chemotherapy and sequential TRT, and 1 patient was treated with etoposide–carboplatin and concurrent TRT. Chemotherapy alone was administered in 4 of the 13 patients. Two patients were subjected to surgery followed by chemotherapy. Four patients did not receive intensive therapy.

Treatment Delivery

The treatment plan consisted of an initial cycle of concurrent chemoradiotherapy followed by three cycles of consolidation chemotherapy (Table 3). All patients received the same chemotherapy regimen of cisplatin at 40–80 mg/m^2 on day 1 combined with etoposide at 80–100 mg/m^2 on days 1–3.

Table 1. Characteristics of the study cohort

Patient	Age/sex	TNM stage	PS	Complications	Smoking history
1	70/M	T2N1M0	1	HT	20/day × 50 years
2	70/M	T3N1M0	0	Berger disease, old TB	40/day × 50 years
3	71/M	T3N2M0	0	DM, bladder cancer	20/day × 50 years
4	71/M	T1N2M0	1	Harada disease	20/day × 50 years
5	72/F	T2N2M0	1	HT, old TB, asthma, one kidney	20/day × 35 years
6	72/M	T1N2M0	0	HT, hyperlithuria	10/day × 50 years
7	73/M	T1N2M0	1	HT	25/day × 60 years
8	76/M	T2N1M0	0	None	20/day × 50 years
9	77/F	T3N0M0	1	Deafness	15/day × 57 years
10	78/M	T3N0M0	0	DM, ASO, old TB	20/day × 58 years
11	79/F	T2N2M0	1	None	None
12	79/F	T1N2M0	0	HT	5/day × 50 years

PS, Eastern Cooperative Oncology Group performance status; HT, hypertension; TB, tuberculosis; DM, type 2 diabetes mellitus; ASO, arteriosclerosis obliterans.