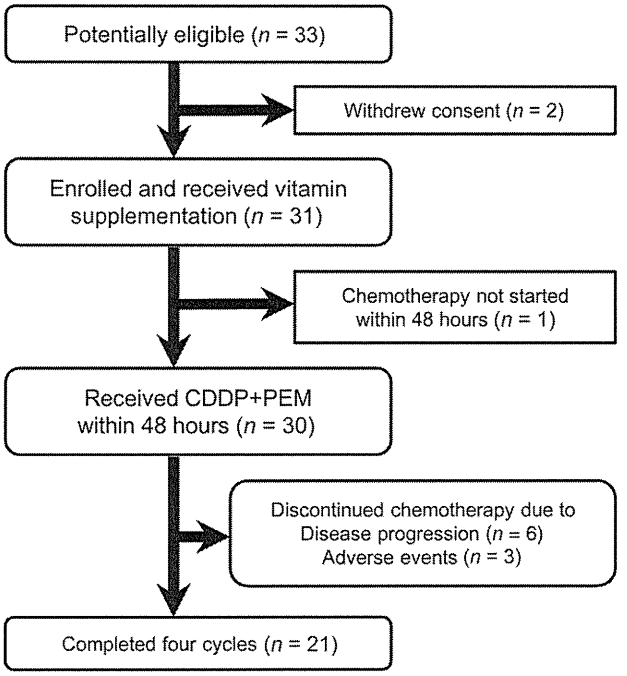

Figure 1. Flowchart of the study.
Abbreviations: CDDP, cisplatin; PEM, pemetrexed.

Table 2. Toxicities observed in this study

Toxicity	G1, *n*	G2, *n*	G3, *n*	G4, *n*	≥G3, %
Hematologic					
Neutropenia	8	7	2	0	7
Leukopenia	8	8	1	0	3
Anemia	14	6	2	0	7
Thrombocytopenia	9	0	0	0	0
Nonhematologic					
ALT increased	16	1	0	0	0
AST increased	8	0	0	0	0
Creatinine increased	5	0	0	0	0
Anorexia	15	8	0	0	0
Nausea	15	8	0	0	0
Fatigue	11	0	0	0	0
Diarrhea	3	1	1	0	3
Infection (lung, gum)	0	2	0	0	0
Rash	2	0	0	0	0
Neuropathy, sensory	2	0	0	0	0
Hypertension	0	0	1	0	3
Myocardial infarction	—	0	1	0	3
Thromboembolic event	0	0	1	0	3
Stroke	0	1	0	0	0
Vomiting	1	0	0	0	0
Stomatitis	1	0	0	0	0
Febrile neutropenia	—	—	0	0	0

Abbreviations: —, grade is not available; ALT, alanine aminotransferase; AST, aspartate aminotransferase; G, grade (according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0).

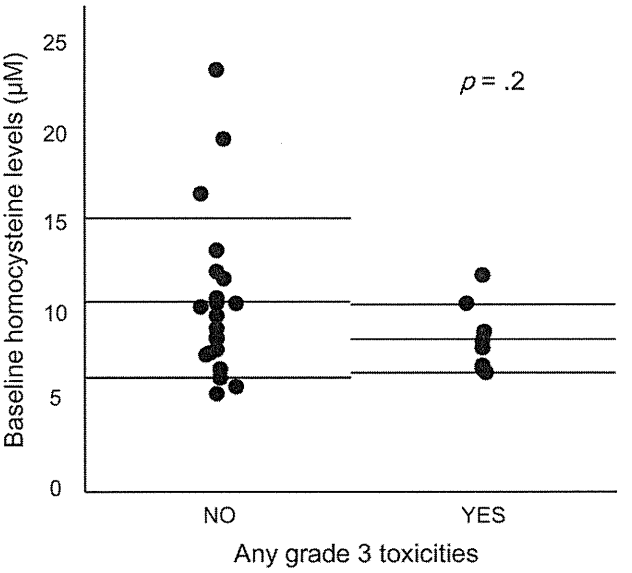

Figure 2. Baseline homocysteine concentrations and grade 3 toxicities. The three horizontal lines in each column represent the following: upper, mean plus SD; middle, mean; bottom, mean minus SD.

toxicities caused by PEM, was not correlated with adverse events in this study. This noncorrelation suggests the efficacy of short-term vitamin supplementation.

Vitamin supplementation in the JMDB study [15] was started 1 to 2 weeks before the first dose of PEM, and CDDP + PEM was repeated every 3 weeks for a maximum of 6 cycles. In East Asian patients who received CDDP + PEM, neutropenia grade ≥3, other laboratory toxicities grade ≥3, and non-laboratory toxicities grade ≥3 were observed in 27.7%, 32.3%, and 15.4%, respectively [14]. The incidence of toxicities in our study was lower than in this historical cohort, probably because of the smaller number of maximum treatment cycles (four) applied in our study. A recently published single-institute study in Japan evaluating CDDP + PEM therapy with standard vitamin supplementation reported incidences of neutropenia grade ≥3 and any nonhematologic toxicities grade ≥3 of 16% and 14%, respectively [16]; thus, the overall toxicity profile of that trial was similar to that of our study.

The response rate and PFS for CDDP + PEM therapy were 46.5% and 6.4 months, respectively, in the East Asian subset of the JMDB study [14], and 44% and 4.3 months, respectively, in the Japanese single-institute phase II trial [16]. These values are similar to those of our study. As in the previously mentioned phase III study of mesothelioma [5], the alteration in vitamin supplementation did not affect the antitumor efficacy of CDDP + PEM.

In our study, the baseline tHcy concentrations of patients with toxicities grade ≥3 were not elevated compared with those in patients without toxicities grade ≥3. As mentioned earlier, tHcy concentrations are increased in the presence of vitamin B_{12} and/or folate deficiency [17]. In cases of PEM treatment without vitamin supplementation, high tHcy concentrations are predictive of severe PEM-related adverse events [4]. The absence of a relationship between baseline tHcy concentrations and toxicities of chemotherapy suggests that, as we speculated, short-term vitamin supplementation is as effective as the standard 1-week supplementation. One

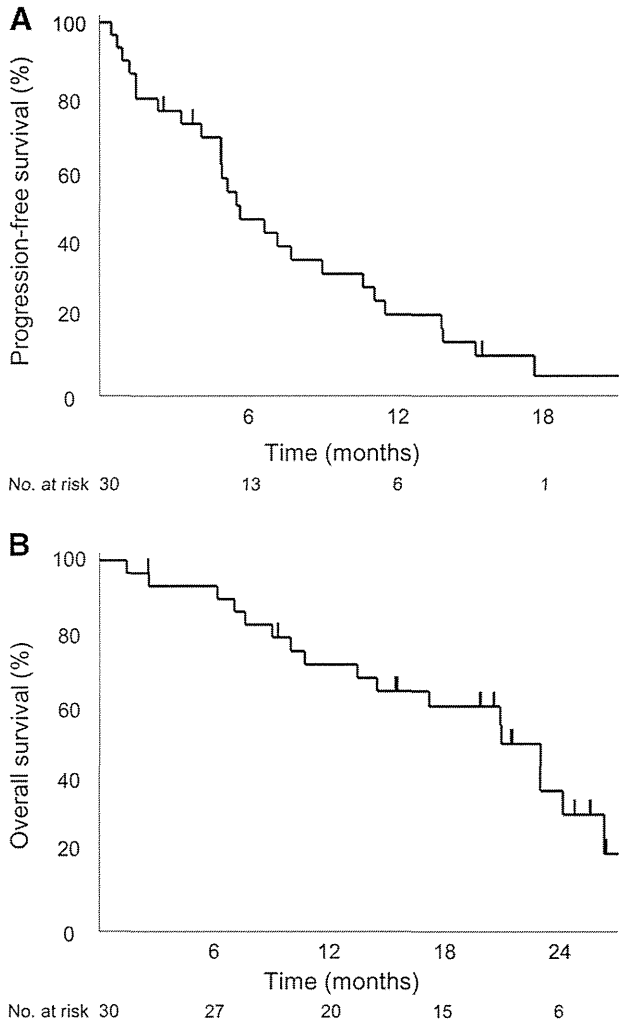

Figure 3. Kaplan–Meier curves for progression-free survival **(A)** and overall survival **(B).**

grade 3 venous thromboembolic event and one grade 3 arterial thrombosis (myocardial infarction) occurred in our study. These toxicities were recognized as attributable to CDDP [18] and were likewise observed in the CDDP + PEM arm of the phase III trial of necitumumab [19].

The key limitation of this nonrandomized study is the potential of involving selection bias, such as ethnic variation. We attempted to minimize bias by adopting the East Asian subset of a previous large phase III study and by performing additional comparisons with a Japanese cohort. Although some studies indicate that average intake of folic acid is lower in Europe than in the United States and Japan [20–22], we found that baseline folate status was not correlated with toxicities of PEM with shortened vitamin supplementation. The safety of our procedure for patients with an increased risk of folate deficiency, such as patients with poor PS or heavily pretreated patients, is yet to be validated. Another limitation is the small sample size of our study. A large randomized trial is generally warranted for establishing a standard treatment, but it is often difficult to conduct such a trial among many competing trials of new therapeutic agents. The sample size was calculated by using the best available data at the time of study planning, to have a sufficient statistical power. However, because PEM is a well-tolerated drug and has a low incidence of severe adverse events, a larger sample size is needed for detecting uncommon toxicities and generalizing our procedure. A pragmatic study for up to 140 participants, including heavily pretreated patients, is currently under way (UMIN000010570).

Although clinical trials have strict eligibility criteria, some enrolled patients experience disease progression before receiving the study treatment [5, 15]. Because PEM-based therapy is an indispensable part of standard chemotherapy [15, 23], failure to start the regimen can have a negative impact on patient outcomes. Our procedure enables earlier administration of standard chemotherapy, potentially avoiding problems associated with rapid disease progression before the initiation of chemotherapy. A retrospective analysis of a study evaluating PEM monotherapy for small-cell lung cancer with full folic acid supplementation showed no significant difference in toxicity among patients who received vitamin B_{12} injections ≥7 days ($n = 86$), 4 to 6 days ($n = 18$), or 0 to 3 days ($n = 12$) before starting PEM [24]. However, we believe that the lead-in time before the first dose of PEM should not be shortened to <24 hours, given that there is no pharmacokinetic rationale for this and that the number of patients who received vitamin B_{12} injection within 24 hours before the first dose of PEM is unknown.

Conclusion

Administration of CDDP + PEM after a shortened period of vitamin supplementation is well tolerated and retains antitumor efficacy. Analysis of baseline tHcy concentrations confirmed the efficacy of short-term vitamin supplementation. Our findings indicate that a shortened period of vitamin supplementation is a rational option in clinical practice.

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Disclosures

Yukio Hosomi: Eli Lilly, Taiho Pharmaceutical, Chugai, AstraZeneca (H); Eli Lilly, Yakult, MSD, Kyowa Kirin, Daiichi Sankyo, Chugai (RF). The other authors indicated no financial relationships.

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Original Articles

A Feasibility Study of Carboplatin Plus Irinotecan Treatment for Elderly Patients with Extensive Disease Small-cell Lung Cancer

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Objective: The role of platinum agents plus irinotecan has been unclear for elderly patients with extensive disease small-cell lung cancer. We conducted a feasibility study to evaluate the safety and efficacy of carboplatin plus irinotecan in preparation for a planned Phase III study.
Methods: Based on another Phase I study, carboplatin area under the curve of four Day 1 plus irinotecan 50 mg/m^2 Days 1 and 8 every 3 weeks for four courses was administered. Patients aged ≥70 years with a performance status of 0–2 were eligible. The primary endpoint was feasibility, defined as the percentage of patients who have received three or more courses of chemotherapy. If the feasibility was ≥60% in the first 10 patients, this endpoint would be considered to be met.
Results: Eleven patients were registered. The median age was 77 years, and nine patients had a performance status of 1. Ten patients completed four courses of treatment, and neither dose omission nor modification was required. The feasibility was 91% (10/11) and the relative dose intensity was 76.9%. Because neutropenia was frequently prolonged, the next course was delayed in 53% of all courses. Other toxicities were generally mild, and the only Grade 4 toxicity was hyponatremia. The overall response rate was 90% (9/10), and the progression-free survival and the overall survival were 5.1 and 10.9 months, respectively.
Conclusions: This regimen appears to be feasible and effective. Based on these results, a Phase II/III trial comparing carboplatin plus etoposide with carboplatin plus irinotecan for elderly patients with extensive disease small-cell lung cancer is being planned by the Japan Clinical Oncology Group.

Key words: chemo-respiratory tract – chemo-Phase I–III – clinical trials – lung medicine

INTRODUCTION

Approximately 30–40% of patients with small-cell lung cancer (SCLC) are ≥70 years old, and the proportion of elderly SCLC patients is continuously increasing in Japan (1–3). However, as elderly patients have been frequently excluded from clinical trials, no standard chemotherapeutic regimen has been established for this patient population. Moreover, standard chemotherapeutic regimens for non-elderly SCLC patients are not always suitable for older patients due to their vulnerable organ function and/or co-morbidities. Therefore, the establishment of a chemotherapeutic regimen that is well balanced between safety and efficacy for this population should be pursued.

The Japan Clinical Oncology Group (JCOG) 9702 study compared carboplatin plus etoposide (CE) versus split-dose cisplatin plus etoposide (SPE) in elderly and poor-risk patients with extensive disease (ED)-SCLC (4). Based on the results of this study, the JCOG concluded that the SPE regimen should remain as the standard treatment for elderly and poor-risk patients with ED-SCLC, the CE regimen being an alternative. However, because the CE regimen does not require hydration and can be administered in an outpatient setting, elderly patients with ED-SCLC in Japan more commonly receive this regimen.

In contrast, the Phase III JCOG 9511 study has shown that irinotecan plus cisplatin (IP) is more effective than etoposide plus cisplatin (EP) for treating non-elderly patients with ED-SCLC (5). However, elderly patients (age $\geq$71 years) were excluded from this trial. When considering the treatment plan for elderly patients with ED-SCLC, the 1-day bolus administration of this cisplatin-based regimen would be difficult because hydration is required. Until now, the carboplatin plus irinotecan (CI) regimen has been repeatedly reported. Although several studies included patients 70 years of age or older, few studies were especially designed for the elderly. Therefore, it would be meaningful to consider a CI regimen for the elderly. Two randomized trials have compared CI with CE for ED-SCLC patients. Although Schmittel et al. (6) did not show a significant survival benefit in the CI arm, survival was marginally better and fewer hematological toxicities were observed. In contrast, Hermes et al. (7) reported a significant survival advantage of CI over CE. Although these trials were not specifically designed for elderly patients and the doses used differed from Japanese standard doses, we believed it was worthwhile to investigate the efficacy of CI in elderly patients with ED-SCLC. Furthermore, a recent meta-analysis of camptothecins compared with etoposide in combination with platinum in ED-SCLC showed a survival benefit associated with camptothecins plus platinum (excluding nogitecan) over etoposide plus platinum in a subgroup analysis (8). Thus, a Phase III trial comparing CE with CI in elderly patients with ED-SCLC is being warranted in the JCOG Lung Cancer Study Group (LCSG).

In our previous study (9), we reported the 4-weekly schedule of CI regimen using prophylactic granulocyte colony-stimulating factor (G-CSF) support in elderly patients with SCLC. However, this study was not a Phase I study and had a heterogeneous patient population. In addition, because not only chemotherapy-naïve but also pretreated patients were included and the treatment drug dose was changed according to the patient's characteristics, the recommended dose could not be decided in the study. Recently, prophylactic use of G-CSF has not been preferred in clinical practice in Japan because more expensive cost and prolonged hospital stays are required. For the reason given above, we cannot apply the previous data to plan the Phase III study and we think that optimal schedule and dose of CI for elderly patients with SCLC have not been established. On the other hand, Thoracic Oncology Research Group (TORG) decided a recommended dose of 3-weekly schedule of CI regimen for elderly patients with limited disease (LD)-SCLC in a Phase I study (unpublished data). Because thoracic radiotherapy was sequentially administered after four courses of chemotherapy in this Phase I study, it might be justified that the recommended dose of CI for LD-SCLC could be used in elderly patients with ED-SCLC based on these data. Furthermore, because members of JCOG and TORG were much different, JCOG-LCSG recommended a further feasibility study by only JCOG members for elderly patients with ED-SCLC. Therefore, we conducted a feasibility study to evaluate the safety and efficacy of CI in elderly patients with ED-SCLC in preparation for a future JCOG Phase III study designed to compare CE with CI in this patient population. This study is registered with the UMIN Clinical Trials Registry as trial 000003208.

PATIENTS AND METHODS

Patient Selection

Patients with the following inclusion criteria were enrolled: age $\geq$70 years; cytologically or histologically confirmed SCLC; ED stage (defined as at least one of the following: distant metastasis, contralateral hilar-node metastasis, malignant pleural effusion and pericardial effusion); no prior chest radiotherapy or chemotherapy; an Eastern Cooperative Oncology Group performance status (PS) of 0–2; no other co-existing malignancy and adequate hematologic, hepatic and renal organ function (leukocyte count $\geq$4000/mm^3, absolute neutrophil count [ANC] $\geq$2000/mm^3, platelet count $\geq$100 000/mm^3, hemoglobin level $\geq$9.0 g/dl, aspartate aminotransferase [AST]/alanine aminotransferase [ALT] levels $\leq$2$\times$ upper limit of normal range, total bilirubin $\leq$1.5 mg/dl, creatinine $\leq$1.5 mg/dl, creatinine clearance $\geq$50 ml/min and $PaO_2 \geq$ 60 mmHg). The additional criteria were: no symptomatic pericardial or pleural effusion requiring drainage, no active concomitant malignancy, no senile dementia, no diarrhea and provision of written informed consent. The exclusion criteria included brain metastases requiring radiotherapy, superior vena cava syndrome requiring radiotherapy and serious medical or psychiatric illness. Patients with interstitial pneumonitis detected by chest computed tomography (CT) scan were excluded. All the patients had chest X-ray, CT scan of the chest and abdomen, CT scan or magnetic resonance imaging of the brain and isotope bone scanning or positron emission tomography within 28 days before registration.

Treatment Plan

Based on our previous feasibility study using CI for elderly patients with SCLC (9), the TORG conducted a Phase I study of the CI regimen and sequential thoracic radiotherapy for elderly patients with LD-SCLC. In that study, the recommended dose was carboplatin area under the curve (AUC) of four Day 1 and irinotecan 50 mg/m^2 Days 1 and 8 every 3 weeks (unpublished data). Although the TORG study

included only elderly patients with LD-SCLC, we elected to use the recommended dose from this study in the current study of elderly patients with ED-SCLC. Thus, all the patients were assigned to carboplatin AUC 4 intravenously (IV) on Day 1 plus irinotecan 50 mg/m^2 IV on Days 1 and 8 every 21 days. Irinotecan on Day 8 was withdrawn if leukocyte counts were $<3000/mm^3$, platelet counts were $<100\,000/mm^3$ or if diarrhea Grade ≥ 1 occurred. Treatment was repeated for up to four cycles. Subsequent cycles were permitted only if the ANC was $\geq 1500/mm^3$, the leukocyte count was $\geq 3000/mm^3$, the platelet count was $\geq 100\,000/mm^3$, serum creatinine was ≤ 1.57 mg/dl, AST/ALT levels were $\leq 2.5\times$ upper limit of normal range, PS was 0–2, neither infection nor fever was present and treatment-related non-hematologic toxicities (excluding alopecia) had resolved to Grade ≤ 2 after Day 21. A treatment delay of ≤ 2 weeks was permitted. Use of G-CSFs was recommended in accordance with their package inserts or clinical recommendations. If G-CSF therapy was administered, the criteria for the next cycle had to be satisfied both after Day 21 and ≥ 2 days after discontinuation of G-CSF. Antiemetic prophylaxis with 5-HT_3 antagonists plus dexamethasone was routinely administered. Dose modifications were allowed only once if Grade 4 leukopenia or neutropenia lasting ≥ 4 days, Grade 4 thrombocytopenia or Grade 3 non-hematological toxicities, except for nausea/vomiting, constipation, hyponatremia and creatinine, occurred. When dose modification was needed, the next treatment course was started with carboplatin AUC 4 on Day 1 plus irinotecan 40 mg/m^2 on Days 1 and 8 every 21 days.

The protocol treatment was terminated if any of the following occurred: disease progression, a treatment delay ≥ 2 weeks, need for dose modification two times, Grade 2–4 pneumonitis and Grade 4 non-hematological toxicities. Because this was a feasibility study, post-protocol treatments were left to the discretion of the treating physicians.

Study Design

This trial was designed as a multicenter prospective feasibility study. The study protocol was approved by the institutional review board at each institution prior to study initiation. The primary objective was feasibility, defined as the percentage of patients who have received three or more courses of chemotherapy. Patients showing disease progression prior to receiving three courses of chemotherapy were excluded from the feasibility evaluation. In addition, even if irinotecan was not administered on Day 8 due to toxicity, the chemotherapy course was judged as being complete. In the JCOG9702 (4), the percentages of patients who have received three and four courses of CE regimen were 69 and 63%, respectively. In this study, we considered that the completion rate of three or more courses of chemotherapy was a more appropriate endpoint than that of four courses because CI regimen might be more toxic than the CE regimen. Therefore, we concluded that the study treatment was feasible when the completion rate of three or more courses of chemotherapy was $\geq 60\%$. Ten patients were initially registered into this study. If the feasibility (completion rate) was $>60\%$, the study would be considered to have yielded positive results and to be finished. If the completion rate was 30 to $<60\%$, we planned to enroll 10 more patients to confirm whether the low rate was due to the treatment regimen or to chance. If the feasibility remained at $<60\%$ in a total of 20 patients, the study would be considered to have yielded negative results. The secondary objectives were toxicity status, overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors criteria, version 1.0. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria version 3.0.

If a patient was documented as having a complete response (CR) or a partial response (PR), a confirmatory evaluation was performed after an interval of at least 4 weeks. The patient was considered to have a stable disease (SD) if it was confirmed and sustained for 6 weeks or longer.

The relative dose intensity (RDI) of irinotecan was calculated by dividing the actual received dose of the agent among all chemotherapy courses (mg/m^2/week) by the total projected dose of the four treatment courses (mg/m^2/week).When chemotherapy was completed without any delays or skipping of agents, the RDI was 100%.

Table 1. Patient characteristics

Median age, years (range)	77.5 (70–82)
Gender	
Male/female	10/0
ECOG PS 0/1	1/9
TNM classification	
T 4/3/2/1	4/2/1/3
N 0/1/2/3	1/1/2/6
M 0/1	1/9
Brinkman index	
Median (range)	1110 (840–3000)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

RESULTS

Patient Characteristics

From March 2010 through March 2011, 11 patients were registered in three institutions. One patient withdrew consent after Day1 of the first course. Because this patient did not experience acute toxicities and the reason seemed to be related to other personal problems, we thought one more additional patient to the previously scheduled 10 patients were appropriate for this study. The median age was 77 (range, 70–82) years and nine patients had a PS of 1, all of whom were male (Table 1). The median Brinkman Index was 1110 (range,

840–3000). A patient with M0 had a contralateral hilar lymph node metastasis.

Drug Delivery and Dose Intensity

Except for the one patient who withdrew consent, all the patients completed four courses of treatment and no omission of irinotecan on Day 8 occurred (Table 2). Furthermore, no patients required dose modifications. Because the completion rate was 91% (10/11), the primary endpoint of a ≥60% completion rate was met. The RDI of irinotecan was 76.9%. The median course delays between the first and second courses, second and third courses and third and fourth courses were 8.5 (range, 2–11) days, 5.5 (range, 0–10) days and 6.5 (range, 0–17) days, respectively. Of a total of 30 courses, the reasons for chemotherapy delay of ≥4 days were leukopenia or neutropenia in 15 patients (50%) and thrombocytopenia and leukopenia in one patient (3%). Delays caused by bed scheduling at participating institutions occurred in six cases (20%).

Toxicities

Toxicity profiles are shown in Table 3. Both hematological and non-hematological toxicities were generally mild. The only Grade 4 toxicity was hyponatremia in one patient. Grade 3 ANC, hemoglobin and thrombocytopenia occurred in six (60%), one (10%) and two (20%) patients, respectively. G-CSF was administered to three patients. No treatment-related deaths occurred during the study.

One patient suffered from pneumonia during his first course of chemotherapy. He received antibiotic therapy for 7 days and fully recovered. He did not experience infection in subsequent protocol treatment cycles.

Another patient suffered from Grade 4 hyponatremia (117 mEq/l) during his first course of chemotherapy. He did not have any history of renal dysfunction and was considered to have syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a paraneoplastic syndrome. Appropriate intravenous crystalloid infusion facilitated full recovery, and he was able to continue chemotherapy. Severe hyponatremia was not observed in his subsequent protocol treatment cycles.

Table 2. Additional days required in each course and the reasons for delays

Patient no.	Courses 1 and 2	Courses 2 and 3	Courses 3 and 4
1	+7[a]	+10[a]	+11[a]
3	+8[a]	+4[a]	+8[a]
4	+7[b]	+7[b]	+6[b]
5	+11[b]	+7[b]	0[d]
6	+11[a]	+4[a]	+7[a]
7	+8[c]	+9[b]	+2[d]
8	+9[a]	0[d]	+13[a]
9	+2[d]	0[d]	0[d]
10	+11[a]	+2[d]	+1[d]
11	+11[a]	+8[a]	+17[a]
Median delays (range)	8.5 (2–11)	5.5 (0–10)	6.5 (0–17)

Relative dose intensity = 76.9%.
[a]Leukocytopenia.
[b]No available bed.
[c]Leukocytopenia/thrombocytopenia.
[d]No delay or delay within 2 days.

Efficacy

Nine patients achieved PR and one patient experienced SD, yielding an ORR of 90%. The median PFS was 5.1 months (95% confidence interval [CI]: 3.9–5.8; Fig. 1), and the median OS was 10.9 months (95% CI: 7.6–16.8; Fig. 2).

Second-Line Therapy

A total of 9 patients received second-line chemotherapy. The most commonly administered agent was amrubicin ($n = 7$). Other regimens included nogitecan ($n = 1$) and CI ($n = 1$). Palliative chest radiotherapy was administered to one patient. Only one patient did not receive second-line chemotherapy, due to poor PS.

Table 3. Toxicity (worst of any course)

	Grade		
	2	3	4
Hematological			
Leukopenia	3	3	0
Neutropenia	2	6	0
Anemia	5	1	0
Thrombocytopenia	2	2	0
Non-hematological			
High AST/ALT	1	0	0
Creatinine	0	0	0
Nausea	2	0	0
Vomiting	0	0	0
Diarrhea	3	0	0
Constipation	1	0	0
Pneumonitis	0	0	0
Bleeding	0	0	0
Infection	0	1	0
Hyponatremia	0	0	1
Peripheral neuropathy	1	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

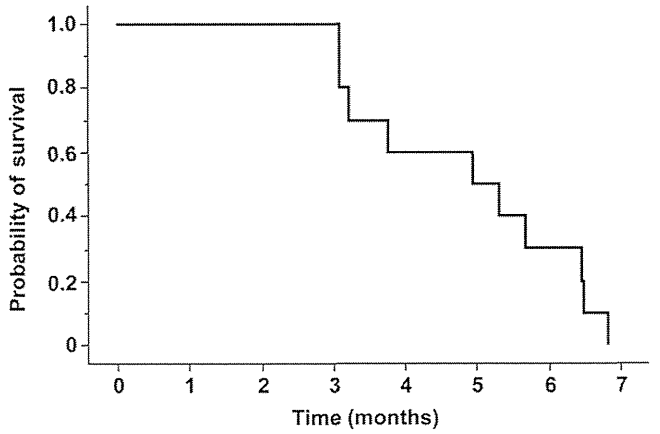

Figure 1. Progression-free survival. Median: 5.1 months (95% confidence interval [CI]: 3.9–5.8).

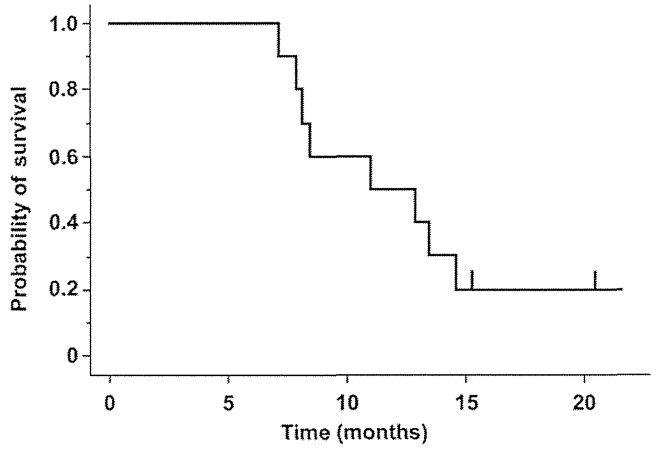

Figure 2. Overall survival. Median: 10.9 months (95% CI: 7.6–16.8).

DISCUSSION

Standard treatment for elderly patients with ED-SCLC has been controversial until now. Moreover, no global treatment consensus for these elderly patients has yet been reached. Because the median age of lung cancer patients is increasing in Japan, the need to formulate a strategy for treating this population is urgent. Some trials have shown that irinotecan might be a key drug for SCLC, particularly among Asian individuals (5,9); therefore, we conducted this feasibility study of CI in elderly SCLC patients. In this study, except for one patient who withdrew consent for chemotherapy, all other patients completed four courses of protocol treatment and the primary endpoint was met, with a feasibility of 91% (10/11). The toxicities were tolerable in this study. In general, Grade 4 hematologic toxicities are commonly experienced in association with chemotherapy for SCLC, even in patients with a good PS and adequate organ function (4–9). Only one patient in the present study experienced Grade 4 hyponatremia, and no Grade 4 hematologic toxicities were observed. The low frequency of diarrhea is particularly interesting. While the JCOG 9511 study comparing IP with EP (5) showed that the frequency of diarrhea associated with the IP regimen was relatively high (16%), no Grade 3 or 4 diarrhea was observed in the present study. Although the reason for this low frequency of diarrhea remains unclear, the low dose of irinotecan used (50 mg/m^2, Days 1 and 8) might have been a contributing factor.

While no CRs were observed, the 90% (9/10) response rate was satisfactory. Moreover, both OS and PFS were slightly longer than those observed in both treatment arms of JCOG 9702, which had almost the identical eligibility criteria (4). These data suggest that the CI regimen might improve outcomes of elderly patients with ED-SCLC. Two possible reasons may explain the promising efficacy observed in this trial. First, amrubicin was administered to 70% of patients as second-line chemotherapy. This agent was not administered at the time of the JCOG 9702 study. Because some investigators reported that second-line amrubicin was effective in relapsed SCLC (10–13), the use of this agent might have positively impacted on survival in this study. Secondly, all of the patients PS of 0–1, even though the eligibility criteria also allowed a PS of 2. In contrast, 26% of patients in the JCOG9702 study had a PS of 2–3 (4). Therefore, patient selection may have also contributed to the prolonged survival and reduced toxicities observed in this study.

This study has several limitations. First, we could have conducted more dose escalation due to the mild toxicity. However, chemotherapy delays occurred frequently, primarily due to neutropenia. Because dose escalation could have potentially caused more severe myelosuppression or delays of chemotherapy administration, we believe that it would have been difficult to escalate the dose in this trial. Secondly, our regimen included relatively low doses compared with the regimens used in non-elderly patients. Administration of irinotecan 50 mg/m^2 Days 1 and 8 every 3 weeks yields a dose intensity of 33 mg/m^2/week. In contrast, the dose intensity of irinotecan (60 mg/m^2, Days 1, 8 and 15, every 4 weeks) was 45 mg/m^2/week in JCOG9511. However, the omission of Day 15 irinotecan occurred in 50% of the courses in JCOG9511 (5). As no omission of Day 8 irinotecan occurred in the present study and course delays only occurred occasionally, the actual difference in dose intensity between the present trial and JCOG9511 may be relatively small. Thirdly, this feasibility study had a small sample size. Further investigation with a larger number of patients is warranted to verify the current results. Fourthly, this trial was not designed based upon an appropriate statistical method. However, if this study was done as a Phase II study using a Simon Minimax design, ~30–40 patients were required. At the time of study initiation, we felt that CI regimen became a promising experimental arm for a future Phase III trial based on our previous study. In addition, many JCOG members hesitated to perform a time-consuming Phase II trial of CI regimen. Therefore, we evaluated the feasibility of this regimen using a small sample size of 10 patients. If a marginal result for feasibility was obtained in the first 10 patients, additional 10 patients were required to avoid a negative result by chance.

In conclusion, treatment with CI in elderly ED-SCLC patients is feasible and appears to provide less toxicities and more efficacy than other regimens. Based on the current study, a Phase II/III trial comparing CE with CI in elderly patients with ED-SCLC is being scheduled by the JCOG LCSG.

Funding

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Conflict of interest statement

None declared.

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Etoposide and cisplatin versus irinotecan and cisplatin in patients with limited-stage small-cell lung cancer treated with etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy (JCOG0202): a randomised phase 3 study

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Summary

Background Four cycles of etoposide plus cisplatin and accelerated hyperfractionated thoracic radiotherapy (AHTRT) is the standard of care for limited-stage small-cell lung cancer (SCLC). Irinotecan plus cisplatin significantly improved overall survival compared with etoposide plus cisplatin for extensive-stage SCLC. We compared these regimens for overall survival of patients with limited-stage SCLC.

Methods We did this phase 3 study in 36 institutions in Japan. Eligibility criteria included age 20–70 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and adequate organ functions. Eligible patients with previously untreated limited-stage SCLC received one cycle of etoposide plus cisplatin (intravenous etoposide 100 mg/m² on days 1–3; intravenous cisplatin 80 mg/m² on day 1) plus AHTRT (1·5 Gy twice daily, 5 days a week, total 45 Gy over 3 weeks). Patients without progressive disease following induction therapy were randomised (1:1 ratio, using a minimisation method with biased-coin assignment balancing on ECOG performance status [0 *vs* 1], response to induction chemoradiotherapy [complete response plus near complete response *vs* partial response and stable disease], and institution) to receive either three further cycles of consolidation etoposide plus cisplatin or irinotecan plus cisplatin (intravenous irinotecan 60 mg/m² on days 1, 8, 15; intravenous cisplatin 60 mg/m² on day 1). Patients, physicians, and investigators were aware of allocation. The primary endpoint was overall survival after randomisation; primary analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00144989, and the UMIN Clinical Trials Registry, number C000000095.

Findings 281 patients were enrolled between Sept 1, 2002, and Oct 2, 2006. After induction etoposide plus cisplatin and AHTRT, 258 patients were randomised to consolidation etoposide plus cisplatin (n=129) or irinotecan plus cisplatin (n=129). In the etoposide plus cisplatin group, median overall survival was 3·2 years (95% CI 2·4–4·1). In the irinotecan and cisplatin group, median overall survival was 2·8 years (95% CI 2·4–3·6); overall survival did not differ between the two groups (hazard ratio 1·09 [95% CI 0·80–1·46], one-sided stratified log-rank p=0·70). The most common adverse events of grade 3 or 4 were neutropenia (120 [95%] in the etoposide plus cisplatin group *vs* 101 [78%] in the irinotecan plus cisplatin group), anaemia (44 [35%] *vs* 50 [39%]), thrombocytopenia (26 [21%] *vs* six [5%]), febrile neutropenia (21 [17%] *vs* 18 [14%]), and diarrhoea (two [2%] *vs* 13 [10%]). There was one treatment-related adverse event leading to death in each group (radiation pneumonitis in the etoposide plus cisplatin group; brain infarction in the irinotecan plus cisplatin group).

Interpretation Four cycles of etoposide plus cisplatin and AHTRT should continue to be the standard of care for limited-stage SCLC.

Funding National Cancer Center and the Ministry of Health, Labour, and Welfare of Japan.

Introduction

The shift from non-filter to filter tobacco has resulted in a decrease in small-cell and squamous-cell lung cancer, and an increase in adenocarcinoma of the lung.[1] Currently, small-cell lung cancer (SCLC) accounts for 13% of all lung cancer, and about a third of patients with SCLC have limited-stage disease—ie, disease confined to the hemithorax.[2]

Combination chemotherapy is the cornerstone of SCLC treatment, and meta-analyses[3,4] have shown that addition of thoracic radiotherapy to combination chemotherapy significantly improves the survival of patients with limited-stage SCLC. Several randomised trials[5–7] have shown that early use of concurrent thoracic radiotherapy results in improved overall survival compared with sequential or late use when etoposide and cisplatin are used as combination

chemotherapy. The US intergroup phase 3 study[8] showed that accelerated hyperfractionated thoracic radiotherapy (AHTRT) with etoposide plus cisplatin for limited-stage SCLC resulted in significantly improved overall survival compared with standard fractionation, once-daily irradiation, with 5-year survival of 26% and 16%, respectively. Thus, etoposide plus cisplatin and AHTRT is now the standard of care in patients with limited-stage SCLC. However, many patients with limited-stage SCLC experience tumour recurrence and die from the disease, showing the need for improved therapy.

The Japan Clinical Oncology Group (JCOG) previously undertook a randomised phase 3 trial[9] (JCOG9511) comparing irinotecan plus cisplatin with etoposide plus cisplatin in patients with extensive-stage SCLC. Response and overall survival were significantly better for patients treated with irinotecan than those treated with etoposide. The result prompted us to explore the use of irinotecan and cisplatin in limited-stage SCLC. A phase 2 study[10] showed that irinotecan and cisplatin after concurrent etoposide plus cisplatin plus AHTRT for limited-stage SCLC was safe with acceptable side-effects, and the 3-year survival of 38% of patients was encouraging.

Therefore, we did a randomised phase 3 trial to compare overall survival of patients with limited-stage SCLC given three cycles of irinotecan plus cisplatin or etoposide plus cisplatin after one cycle of induction etoposide plus cisplatin and concurrent AHTRT.

Methods

Study design and participants

We did this randomised, open-label, phase 3 study in 36 institutions in Japan (appendix). We enrolled patients with histologically or cytologically confirmed limited-stage SCLC—defined as disease confined to one hemithorax, including ipsilateral hilar, bilateral mediastinal, and bilateral supraclavicular lymph node metastases. Pleural effusion of less than 1 cm width by chest CT was defined as limited-stage disease; malignant pleural effusion was defined as extensive-stage disease and excluded from the study. Additional eligibility criteria consisted of measurable disease, age 20–70 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, no previous treatment for SCLC, no history of anticancer chemotherapy, 4000 leucocytes per μL or greater, 10^5 platelets per μL or greater, haemoglobin of 90 g/L or greater, serum creatinine of 132·60 μmol/L or less, serum bilirubin of 34·21 μmol/L or less, serum aspartate aminotransferase of 100 IU/L or less, serum alanine aminotransferase of 100 IU/L or less, and partial pressure of oxygen of 9·33 kPa or greater. Consultation with a radiation oncologist was mandated before enrolment. We included patients aged between 20 years and 70 years because the previous JCOG trial[9] (JCOG9511) comparing irinotecan and cisplatin with etoposide plus cisplatin for extensive-stage SCLC included only patients aged 70 years or younger.

Exclusion criteria were active concomitant malignancy, active infection, uncontrolled heart disease or a history of myocardial infarction within the previous 6 months, unstable angina, uncontrollable hypertension or diabetes mellitus, interstitial pneumonia or active lung fibrosis on chest radiograph, psychiatric disease, malignant pericardial effusion, diarrhoea, intestinal obstruction or paralysis, and concurrent administration of any oral or intravenous steroid. We excluded pregnant or lactating women.

All patients enrolled in the study underwent an induction therapy of one cycle of etoposide plus cisplatin with concurrent AHTRT, eligible patients were registered again and randomised to consolidation chemotherapy consisting of three cycles of etoposide plus cisplatin or irinotecan plus cisplatin. The second registration eligibility criteria were: within 49 days from the first registration, ECOG performance status of 0–1, 3000 leucocytes per μL or greater, 10^5 platelets per μL or greater, serum creatinine of 132·60 μmol/L or less, serum bilirubin of 34·21 μmol/L or less, serum aminotransferase of 100 IU/L or less, no fever or diarrhoea within 24 h, no pulmonary infiltration beyond the radiation portal, no active infection, radiation dermatitis or oesophagitis of grade 2 or less, completion of induction chemoradiotherapy, no progressive disease, and tumour response to induction chemoradiotherapy as assessed by chest CT (complete response, near complete response, partial response, or stable disease). Because almost all patients with limited-stage SCLC are admitted to hospital during induction chemoradiotherapy in Japan, chest CT assessment within the specified timeframe was not problematic. The assessment of response to chemoradiation was done after day 23, counted from the start of induction chemoradiotherapy.

The study protocol was approved by the Clinical Trial Review Committee of JCOG and the institutional review boards of the participating institutions. All patients provided written informed consent.

Procedures

Induction chemotherapy consisted of intravenous cisplatin 80 mg/m² on day 1 and intravenous etoposide 100 mg/m² on days 1–3. AHTRT was begun on day 2 of induction chemotherapy and administered twice daily, 5 days a week, (1·5 Gy per fraction, with 6 h or more between fractions) to a total dose of 45 Gy in 3 weeks. 30 Gy was delivered with 6–10 MV photons using anterior–posterior opposed fields that included the primary tumour; metastatic lymph nodes; and regional nodes, excluding the contralateral hilar nodes. Supraclavicular lymph nodes were also included when involved. A booster dose of 15 Gy was delivered to the primary tumour and metastatic lymph nodes. Conventional two-dimensional radiograph simulation and three-dimensional CT simulation were allowed for treatment planning; PET scanning was not required. The clinical target volume was equal to the gross tumour volume, including the primary tumour and metastatic nodes (1 cm or greater in shortest dimension).

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See Online for appendix

The planned target volumes for the primary tumour, metastatic lymph nodes, and regional nodes were defined as clinical target volume plus adequate margins (typically 0·5–1·0 cm laterally and 1·0–2·0 cm craniocaudally). The volume of the lung unaffected by cancer to receive 20 Gy or more was kept to 35% or less when three-dimensional CT simulation was used. Lung heterogeneity corrections were not used. If grade 3 non-haematological side-effects (excluding hyponatraemia, nausea, vomiting, and appetite loss), performance status of 3, grade 2 pneumonitis or pulmonary infiltrates, or a fever of 38·0°C or more developed, radiotherapy was withheld until recovery. Quality assurance reviews were done and the results are reported elsewhere.[11]

In the consolidation chemotherapy stage, patients assigned to etoposide plus cisplatin received intravenous cisplatin 80 mg/m² on day 1 and intravenous etoposide 100 mg/m² on days 1–3, repeated every 3 weeks for three cycles. Patients assigned to irinotecan plus cisplatin were treated every 3–4 weeks for three cycles; this regimen consisted of intravenous irinotecan 60 mg/m² on days 1, 8, and 15 and intravenous cisplatin 60 mg/m² on day 1. The doses of cisplatin were the same as in the previous JCOG trial (JCOG9511) in extensive-stage SCLC.[9]

If the leucocyte count decreased to less than 3000 leucocytes per μL or the platelet count fell below 10^5 platelets per μL on the first day of etoposide plus cisplatin or irinotecan plus cisplatin, chemotherapy was withheld until the counts recovered to above these cutoffs. Administration of irinotecan was skipped on day 8 or 15, or on both days, if the leucocyte count was less than 2000 leucocytes per μL, the platelet count was below 10^5 platelets per μL, or if there was any diarrhoea irrespective of grade, or a fever of 37·5°C or more. The dose of etoposide in subsequent cycles was reduced by 20 mg/m² from the planned dose if grade 4 leucopenia, grade 4 thrombocytopenia, or grade 3 non-haematological side-effects (excluding nausea, vomiting, appetite loss, hyponatraemia, and creatinine) developed. The dose of irinotecan in subsequent cycles was reduced by 10 mg/m² from the planned dose if grade 4 leucopenia or grade 4 thrombocytopenia, grade 2 or 3 diarrhoea, or grade 3 non-haematological side-effects (excluding nausea, vomiting, hyponatraemia, and creatinine) developed. The dose of cisplatin was reduced by 10 mg/m² if serum creatinine was higher than 132·60 μmol/L but not exceeding 176·80 μmol/L. Cisplatin was not administered if creatinine was higher than 176·80 μmol/L. Treatment was stopped in patients with non-haematological side-effects of grade 4.

Administration of granulocyte colony stimulating factor (G-CSF) was prohibited on the same days as chemotherapy or radiotherapy. Primary prophylactic G-CSF was not administered. For patients who had developed grade 4 neutropenia or grade 3 febrile neutropenia during previous cycles of chemotherapy, secondary prophylactic G-CSF administration was allowed. Prophylactic antibiotics were not administered.

Prophylactic cranial irradiation (25 Gy in ten fractions) was undertaken for patients showing a complete response or near complete response, defined as a reduction of 70% or more in the sum of the longest diameters of the target lesions.

Before enrolment in the study, each patient provided a complete medical history and underwent physical examination, blood cell count determinations, arterial blood gas, biochemical laboratory examinations, chest radiograph, electrocardiogram, chest CT scan and whole-brain CT or MRI, abdominal ultrasound or CT, and isotope bone scans. Data regarding the time interval between diagnosis and start of concurrent chemoradiotherapy were not collected. Blood cell counts, differential white cell counts and other laboratory data were obtained weekly during induction chemoradiotherapy. All patients were reassessed at the end of consolidation chemotherapy with the same imaging assessments as at the time of enrolment. For efficacy assessments after the end of study treatment, patients were monitored once a month for 1 year and once every 3 months after 1 year. If progression was suspected on the basis of worsening symptoms or abnormal laboratory test values, the site of suspected progression was examined. If recurrence or progression was established, restaging including chest CT, brain MRI or CT, abdominal ultrasound or CT, and bone scintigraphy were done.

Responses were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. Response was defined as the proportion of patients whose best overall response was complete reponse or partial response according to RECIST. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 2.0. Serious adverse events were defined as grade 4 non-haematological or grade 5 adverse events.

Randomisation and masking

After induction chemoradiotherapy, eligible patients were randomly assigned in a 1:1 ratio to receive either three cycles of consolidation etoposide plus cisplatin or irinotecan plus cisplatin at the JCOG Data Center. Randomisation was done using a minimisation method with biased-coin assignment balancing on ECOG performance status (0 *vs* 1), response to induction chemoradiotherapy (complete response plus near complete response *vs* partial response and stable disease) and institution. Patients, treating physicians, and individuals assessing outcomes and analysing data were not masked to treatment allocation.

Statistical analysis

The primary endpoint was overall survival after randomisation. The planned sample size for randomisation was 250 and the expected number of events was 223, with a one-sided α of 2·5% and at least 70% power to detect a difference between groups, assuming 30·0% 3-year survival with etoposide plus cisplatin versus 42·5% with

irionteca plus cisplatin. Final analysis was planned 5 years after completion of accrual. Secondary endpoints were adverse events associated with induction chemoradiotherapy, adverse events associated with consolidation chemotherapy, late radiation morbidity after thoracic irradiation, adverse events during treatment with prophylactic cranial irradiation, incidence of serious adverse events, and progression-free survival after randomisation.

Progression-free survival was calculated from the date of randomisation until the date of documented progression or death (in the absence of progression). Overall survival was calculated from the date of randomisation until the date of death from any cause. Both intervals were estimated by the Kaplan-Meier method.

Three interim analyses were scheduled. The first interim analysis was to assess the futility of the trial after half the planned sample size was randomised. The second interim analysis was planned immediately after patient accrual was completed to decide whether the preplanned follow-up was necessary in terms of efficacy. The third interim analysis was planned 2 years after completion of accrual, with the same aim as the second interim analysis. Results of the interim analyses were reviewed by the JCOG Data and Safety Monitoring Committee and investigators were masked to the results. Multiplicity for analyses of the primary endpoint was adjusted with the O'Brien-Fleming type α-spending function.[12]

The primary endpoint, overall survival after randomisation, was analysed with the log-rank test, stratified by ECOG performance status (0 *vs* 1) and response to induction chemoradiotherapy (complete response plus near complete response *vs* partial response plus stable disease). Hazard ratios (HR) were estimated with a Cox regression model, stratified by the same factors as the log-rank test. Unstratified log-rank tests and unstratified Cox regression models were used for all other analyses. The efficacy analyses were by modified intention to treat, including all patients enrolled at the second registration who did not violate any inclusion criteria. Safety analyses included all patients enrolled at the second registration who received at least one dose of study drug. Analyses were done by the JCOG Data Center using SAS (version 9.2).

This trial was registered with ClinicalTrials.gov, number NCT00144989 and UMIN Clinical Trials Registry, number C000000095.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

281 patients were enrolled between Sept 1, 2002, and Oct 2, 2006. Four patients were shown to be ineligible after the first registration, three did not receive study treatment because of progressive disease, and two did not receive AHTRT, one because of an inappropriate radiation field and one because of an allergy to etoposide (figure 1). After the induction etoposide plus cisplatin plus AHTRT, 258 patients were enrolled at the second registration and

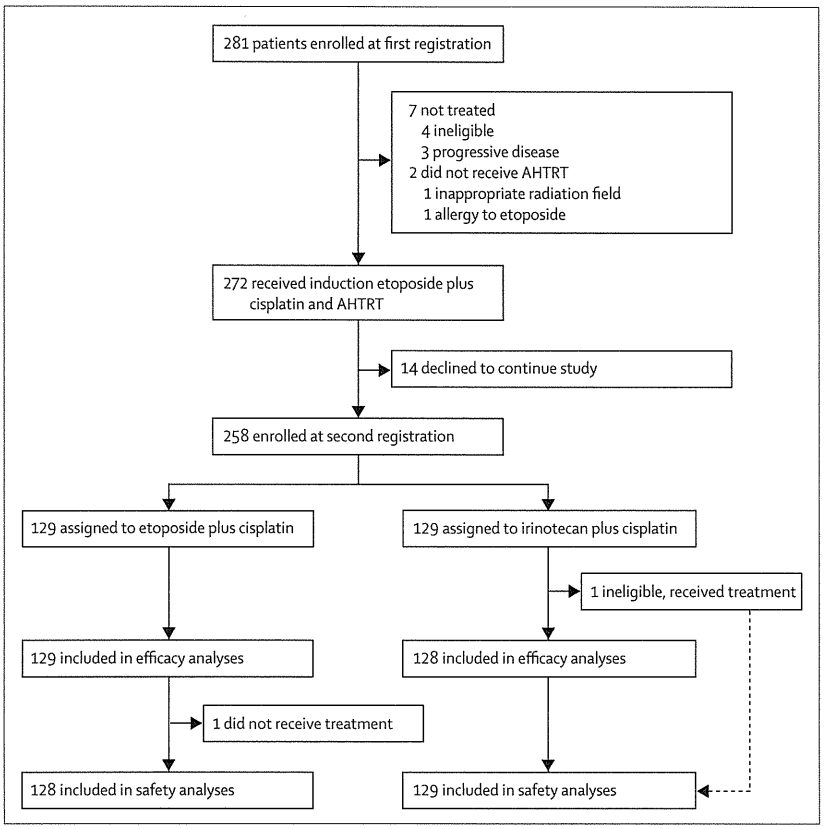

Figure 1: **Trial profile**
AHTRT=accelerated hyperfractionated thoracic radiotherapy.

	First registration (n=281)	Second registration	
		Etoposide and cisplatin (n=129)	Irinotecan and cisplatin (n=129)
Age (years)	61 (32–70)	60 (32–70)	62 (39–70)
Sex			
Men	228 (81%)	103 (80%)	106 (82%)
Women	53 (19%)	26 (20%)	23 (18%)
ECOG performance status			
0	170 (60%)	86 (67%)	85 (66%)
1	111 (40%)	43 (33%)	44 (34%)
Response to induction chemoradiotherapy*			
Complete response	..	3 (2%)	4 (3%)
Near complete response	..	28 (22%)	26 (20%)
Partial response	..	92 (71%)	87 (67%)
Stable disease	..	6 (5%)	12 (9%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *According to Response Evaluation Criteria In Solid Tumors (version 1.0).

Table 1: **Characteristics of patients**

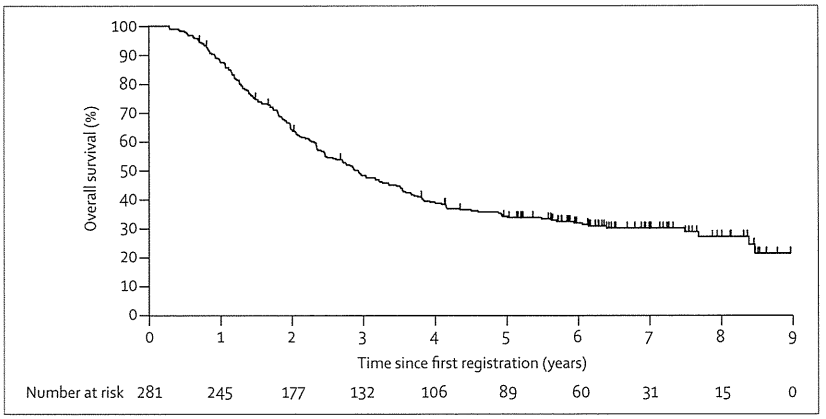

Figure 2: Overall survival after first registration
*One-sided p value from stratified log-rank test, with Eastern Cooperative Oncology Group performance status and response to induction chemoradiotherapy as strata.

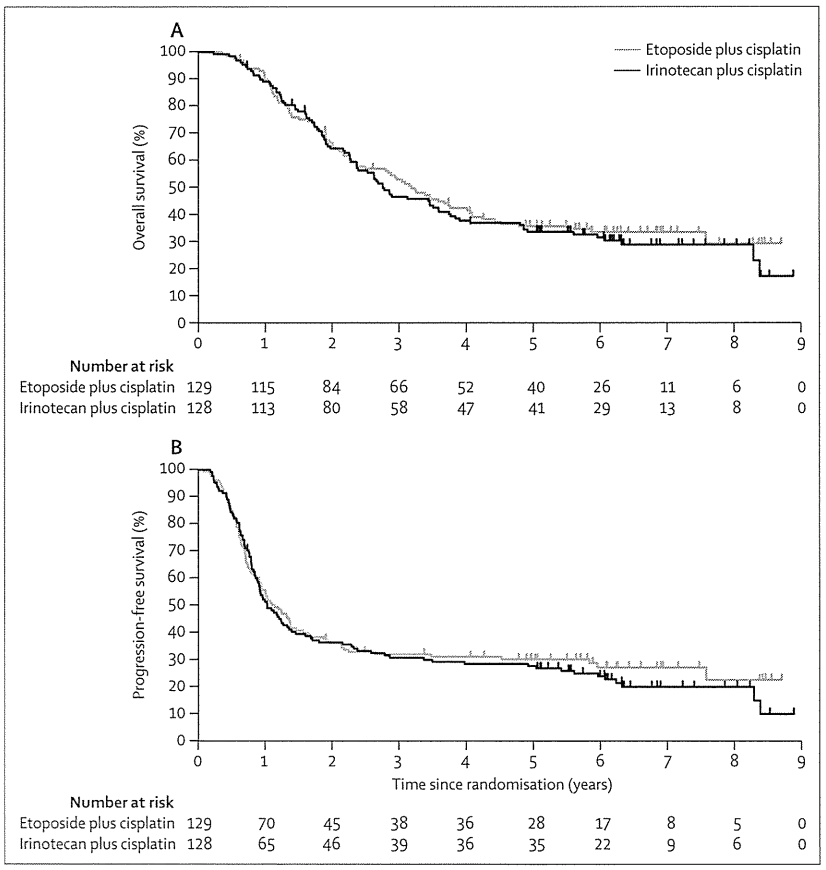

Figure 3: Overall survival (A) and progression-free survival (B) after randomisation
*p value from unstratified log-rank test.

randomised to consolidation etoposide plus cisplatin (n=129) or irinotecan plus cisplatin (n=129). One patient in the irinotecan plus cisplatin group was shown to be ineligible after the second registration because of contralateral hilar node metastasis, this patient was excluded from the efficacy analyses, but included in the safety analyses. Table 1 shows the characteristics of the patients.

Of 129 patients who were randomised to the etoposide plus cisplatin group, 116 patients (90%) received three cycles of consolidation chemotherapy, four (3%) received two cycles, eight (6%) received one cycle, and one (1%) had no consolidation therapy. In the irinotecan plus cisplatin group, 110 of 128 (86%) patients received three cycles of consolidation chemotherapy, six (5%) received two cycles, 12 (9%) received one cycle. The main reasons for non-completion of three cycles of consolidation chemotherapy in the both groups were adverse events (eight patients in the etoposide plus cisplatin group, 12 patients in the irinotecan plus cisplatin group) and patient refusal because of adverse events (nine patients in the etoposide plus cisplatin group, 14 patients in the irinotecan plus cisplatin group); one patient in each group did not complete consolidation chemotherapy because of progressive disease. In the etoposide plus cisplatin group, 115 (89%) of 129 patients received at least 70% of the planned of dose of etoposide, and 116 (90%) of 129 received at least 70% of the planned dose of cisplatin; in the irinotecan plus cisplatin group, 88 (69%) of 128 received at least 70% of the planned dose of irinotecan and 110 (86%) of 128 received at least 70% of the planned dose of cisplatin. Prophylactic cranial irradiation was administered to 76 patients in the etoposide plus cisplatin group and 73 in the irinotecan plus cisplatin group.

Of 281 patients who entered into the first registration, median follow-up for the 88 censored patients was 6·3 years (IQR 5·6–7·2); median overall survival was 2·9 years (95% CI 2·5–3·5), 3-year overall survival was 48·4% (95% CI 42·4–54·1), and 5-year overall survival was 34·3% (28·7–39·9; figure 2). Of 257 patients included in the final analysis of the primary outcome, median follow-up for the 84 censored patients was 6·2 years (IQR 5·4–7·0); there were 173 events. In the etoposide plus cisplatin group, median overall survival was 3·2 years (95% CI 2·4–4·1), 3-year overall survival was 52·9% (95% CI 43·9–61·1), and 5-year overall survival was 35·8% (27·4–44·1). In the irinotecan plus cisplatin group, median overall survival was 2·8 years (95% CI 2·4–3·6), 3-year overall survival was 46·6% (37·7–55·1) and 5-year overall survival was 33·7% (25·5–42·0; HR 1·09 [95% CI 0·80–1·46]; p=0·70 from one sided stratified log-rank test; figure 3A). The results of the unstratified analysis did not differ from those of the stratified analysis (data not shown).

Figure 3B shows the Kaplan-Meier curves for progression-free survival in the two groups. Median progression-free survival was 1·1 years (95% CI 0·9–1·4) in the etoposide plus cisplatin group and 1·0 years (0·9–1·4) in the irinotecan plus cisplatin group (HR 1·10; 95% CI 0·83–1·45; p=0·74 from one sided unstratified log-rank test). In the etoposide group, 3-year progression-free survival was 32·0% (95% CI 24·1–40·1) and 5-year progression-free survival was 30·2% (22·4–38·3). In the irinotecan plus cisplatin group, these were 30·8% (23·0–38·9) and 27·7% (20·2–35·6), respectively.

	Etoposide plus cisplatin plus AHTRT*				Consolidation chemotherapy							
	Grade 1–2	Grade 3	Grade 4	N	Etoposide plus cisplatin				Irinotecan plus cisplatin			
					Grade 1–2	Grade 3	Grade 4	N	Grade 1–2	Grade 3	Grade 4	N
Leucopenia	16 (6%)	148 (54%)	109 (40%)	273	12 (9%)	81 (63%)	34 (27%)	128	28 (22%)	76 (59%)	25 (19%)	129
Anaemia	86 (32%)	1 (<1%)	0	273	76 (59%)	33 (26%)	11 (9%)	128	72 (56%)	42 (33%)	8 (6%)	129
Thrombocytopenia	108 (40%)	20 (7%)	0	273	56 (44%)	22 (17%)	4 (3%)	128	28 (22%)	6 (5%)	0	129
Neutropenia	12 (4%)	57 (21%)	203 (74%)	273	6 (5%)	33 (26%)	87 (68%)	128	28 (22%)	62 (48%)	39 (30%)	129
Hypoalbuminaemia	194 (72%)	0	..	271	102 (80%)	0	..	127	109 (84%)	0	..	129
Bilirubin	72 (26%)	1 (<1%)	0	272	20 (16%)	0	0	128	21 (16%)	0	0	129
Aspartate aminotransferase	54 (20%)	1 (<1%)	0	273	19 (15%)	1 (1%)	0	128	29 (22%)	0	0	129
Alanine aminotransferase	91 (33%)	4 (1%)	0	273	38 (30%)	1 (1%)	0	128	47 (36%)	0	0	129
Creatinine	67 (25%)	0	0	273	55 (43%)	0	0	128	35 (27%)	0	0	129
Fever	75 (27%)	0	0	274	28 (22%)	1 (1%)	0	128	33 (26%)	0	0	129
Alopecia	207 (77%)	..	..	270	94 (76%)	..	..	123	93 (74%)	..	..	126
Weight loss	43 (16%)	0	..	274	17 (13%)	0	..	128	20 (16%)	1 (1%)	..	129
Anorexia	158 (58%)	22 (8%)	1 (<1%)	274	82 (64%)	12 (9%)	0	128	78 (60%)	16 (12%)	0	129
Diarrhoea	28 (10%)	3 (1%)	0	274	10 (8%)	2 (2%)	0	128	68 (53%)	13 (10%)	0	129
Dysphagia–oesophageal†	229 (84%)	5 (2%)	0	274	34 (27%)	0	0	128	34 (26%)	1 (1%)	0	129
Nausea	139 (51%)	17 (6%)	..	274	82 (64%)	7 (5%)	..	128	82 (64%)	7 (5%)	..	129
Stomatitis or pharyngitis	38 (14%)	1 (<1%)	0	274	16 (13%)	0	0	128	15 (12%)	0	0	129
Vomiting	53 (19%)	3 (1%)	0	274	26 (20%)	3 (2%)	0	128	21 (16%)	5 (4%)	0	129
Febrile neutropenia	..	67 (25%)	0	271	..	21 (16%)	0	128	..	18 (14%)	0	129
Infection with grade 3 or 4 neutropenia	0	37 (14%)	0	272	0	15 (12%)	0	128	0	8 (6%)	0	129
Infection without neutropenia	7 (3%)	11 (4%)	1 (<1%)	274	11 (9%)	4 (3%)	0	128	16 (12%)	8 (6%)	0	129
Pneumonitis or pulmonary infiltrates	2 (1%)	1 (<1%)	0	274	9 (7%)	1 (1%)	0	128	16 (12%)	0	0	129

Data were missing for some patients. AHTRT=accelerated hyperfractionated thoracic radiotherapy. *Including two patients who did not undergo radiotherapy. †Related to radiation.

Table 2: **Adverse events**

The two groups did not differ in terms of sites of primary failure. Of 175 patients who had disease progression, in the etoposide plus cisplatin group, 30 had local progression within the radiation field, seven had local progression outside of the radiation field, 26 had progression to the brain, and 35 had systemic progression to other sites; in the irinotecan plus cisplatin group, 27 had local progression within the radiation field, six had local progression outside of the radiation field, 33 had progression to the brain, and 38 had systemic progression to other sites (some patients had progression to more than one site).

In a planned subgroup analysis, women in the etoposide plus cisplatin group had improved overall survival compared with those in the irinotecan plus cisplatin group (median overall survival not reached, 5-year overall survival 55·3% [95% CI 33·8–72·3] *vs* median overall survival 2·4 years [1·6–3·4], 5-year overall survival 26·1% [10·6–44·7] in the irinotecan group; unstratified HR 2·56; 95% CI 1·20–5·44, one-sided p=0·99) whereas outcomes for men did not differ between the groups (0·90; 0·65–1·24, one-sided p=0·25). Other prespecified subgroup analyses, including age (≤60 years old *vs* >60 years old), stage by UICC-TNM 7th edition (≤IIIA *vs* ≥IIIB), ECOG performance status (0 *vs* 1), response to induction chemoradiotherapy (complete response plus near complete response *vs* partial repsonse plus stable disease), bodyweight loss during 6 months (≤5% *vs* >5%), and smoking history (<20 packs per year *vs* ≥20 packs per year) did not differ between the two groups (data not shown).

Of 129 eligible patients randomised to the etoposide plus cisplatin group, 128 (99·2%) had an overall response (24 complete response; 54 near complete response; 50 partial response); of 128 patients in the irinotecan plus cisplatin group, 123 (96·1%) had an overall response (30 complete response; 57 near complete response; 36 partial response).

Table 2 shows side-effects associated with concurrent chemoradiotherapy and consolidation chemotherapy. During consolidation chemotherapy, the most common adverse events of grade 1 or 2 were hypoalbuminaemia (102 [80%] in the etoposide plus cisplatin group *vs* 109 [84%] in the irinotecan plus cisplatin group) and alopecia (94 [76%] *vs* 93 [74%]). The most common adverse events of grade 3 or 4 were neutropenia (120 [95%] in the etoposide plus cisplatin group *vs* 101 [78%] in the irinotecan plus cisplatin group), anaemia (44 [35%] *vs* 50 [39%]), thrombocytopenia (26 [21%] *vs* six [5%]), febrile neutropenia (21 [17%] *vs* 18 [14%]), and diarrhoea (two [2%] *vs* 13 [10%]). 12% of patients in the in the etoposide plus cisplantin group and 6% in the irinotecan plus cisplatin group had infection with grade 3 or 4 neutropenia. However, grade 3 febrile neutropenia did not differ between the two groups. Grade 3 or 4 leucopenia was less frequent in the

Panel: Research in context

Systematic review

Combination chemotherapy is the cornerstone of treatment of small-cell lung cancer (SCLC). We searched PubMed for reports of randomised clinical trials published in English up to Sept 30, 2013, using the terms "lung neoplasms", "small-cell lung cancer", "radiotherapy", and "not non-small-cell lung cancer". We also searched the reference lists of retrieved articles. The quality of evidence was assessed mainly on the basis of whether the standard chemotherapy regimen, etoposide plus cisplatin, was used as the reference group. Meta-analyses[3,4] have shown that addition of thoracic radiotherapy to combination chemotherapy significantly improves the survival of patients with limited-stage SCLC. Several randomised trials[5-7] have shown that early use of concurrent thoracic radiotherapy is better than sequential or late use, when etoposide and cisplatin are used as combination chemotherapy. The US intergroup phase 3 study[8] showed that accelerated hyperfractionated thoracic radiotherapy (AHTRT) with etoposide plus cisplatin for limited-stage SCLC was better than standard fractionation, once-daily irradiation.

Interpretation

At present, standard treatment for patients with limited-stage SCLC is etoposide plus cisplatin with thoracic radiotherapy. AHTRT is recommended when logistically acceptable. As far as we are aware, JCOG0202 is the first randomised trial investigating the efficacy of irinotecan plus cisplatin in patients with limited-stage disease. The hypothesis that irinotecan plus cisplatin could improve overall survial for these patients compared with etoposide plus cisplatin was refuted. Four cycles of etoposide plus cisplatin and concurrent AHTRT should be the standard of care in patients with limited-stage SCLC, and discouragement and cessation of tobacco use is still the most effective strategy to reduce deaths from SCLC.

irinotecan plus cisplatin group than in the etoposide plus cisplatin group; grade 3 or 4 diarrhoea was more frequent in the irinotecan plus cisplatin group than in the etoposide plus cisplatin group (table 2).

Late radiation morbidity after thoracic irradiation did not differ between the two groups (two [1·6%] grade 3 and two [1·6%] grade 4 events in the etoposide plus cisplatin group *vs* two [1·6%] grade 3 events in the irinotecan plus cisplatin group). Only one event [1·3%] of nausea of grade 3 due to prophylactic cranial irradiation was reported in the etoposide and cisplatin group.

Study treatment was terminated because of side-effects in 17 patients (13%) in the etoposide plus cisplantin group and in 26 patients (20%) in the irinotecan plus cisplatin group. There were three treatment-related deaths. One treatment-related death from pneumonitis occurred 86 days after induction chemoradiotherapy (induction etoposide plus cisplantin plus AHTRT). The patient was not randomised because a diffuse interstitial shadow occurred after 28·5 Gy of AHTRT. One patient in the etoposide plus cisplantin group died of radiation pneumonitis 116 days after completion of study treatment. One patient in the irinotecan plus cisplatin group died of brain infarction during the third course of consolidation chemotherapy.

Discussion

In this study of 258 patients with limited-stage SCLC, three cycles of irinotecan plus cisplatin did not improve overall survival compared with three cycles of etoposide plus cisplatin, after one cycle of etoposide plus cisplatin with concurrent AHTRT (panel). Randomisation was done after completion of induction chemoradiotherapy, thus the findings are unlikely to be biased by induction chemoradiotherapy.

JCOG previously reported the results of a randomised phase 3 trial[9] (JCOG9511) comparing irinotecan plus cisplatin versus etoposide plus cisplatin for extensive-stage SCLC. Median overall survival was 12·8 months and 19·5% patients were alive at 2 years in the irinotecan plus cisplatin group, whereas in the etoposide plus cisplatin group, median overall survival was 9·4 months only 5·2% of patients were alive after 2 years (p=0·002 from unadjusted log-rank test). Similar trials[13-15] done mainly in white patients with extensive-stage SCLC, including the Southwest Oncology Group trial[13] (S0124) using almost the same eligibility criteria and identical treatment regimens as JCOG9511, did not confirm the JCOG results. These results suggest pharmacogenomic differences between Japanese and non-Japanese patients.[16] Despite several negative trials, two meta-analyses[17,18] using non-individual-patient data showed a significant survival improvement with irinotecan compared with etoposide in patients with extensive-stage SCLC. However, the efficacy of irinotecan plus cisplatin shown in extensive-stage SCLC was not observed in the Japanese patients with limited-stage SCLC in our current study.

Side-effects were as expected. Severe non-haematological adverse events were much the same between the two groups, except for grade 3 or 4 diarrhoea which occurred in 10% of patients in the irinotecan plus cisplatin group and only 2% of patients in the etoposide plus cisplatin group. Late radiation reactions were not increased in the irinotecan plus cisplatin group. 86% of patients in the irinotecan plus cisplatin group received the planned three cycles of consolidation chemotherapy, and 90% received three cycles in the etoposide plus cisplatin group. Thus, compliance does not explain the negative results in the present study.

5-year overall survival in patients who received standard etoposide plus cisplatin plus concurrent AHTRT has been reported to be 24–26% in two phase 3 studies[7,8] in limited-stage SCLC. Although we failed to show an improvement in survival with our investigational regimen, the 5-year overall survival of 34·3% for all patients in the present study would be the best outcome reported so far. The 5-year overall survival of 55·3% in women who received standard etoposide plus cisplatin consolidation therapy is encouraging. This favourable result might be attributable to selection of patients, such as inclusion of patients with ECOG performance status of 0 or 1, and aged 70 years or younger. However, this selection bias does not fully explain the difference because the proportion of patients with ECOG performance status of 2 in other trials was only about 5%.[7,8] Radiotherapy quality control undertaken in the present study might have contributed to the improved

outcome, because radiotherapy protocol deviations are associated with overall mortality.[11,19] Optimum care of patients, including full disclosure of prognosis in the consent form for the study, might be another factor related to the favourable outcome.[20,21]

Full dose irinotecan cannot be combined with radiotherapy.[22] Thus, it is unlikely that the addition of irinotecan to radiotherapy improves the outcome of patients with limited-stage SCLC who receive combined chemotherapy and radiotherapy treatment. In future trials, new active agents with radiosensitising potential are needed. Testing of different radiotherapy regimens would be another option to improve outcomes in limited-stage SCLC. A randomised trial to establish whether administration of high-dose thoracic radiotherapy, 70 Gy (2 Gy once daily over 7 weeks) or 61·2 Gy (1·8 Gy once daily for 16 days followed by 1·8 Gy twice daily for 9 days), will improve survival compared with 45 Gy (1·5 Gy twice daily over 3 weeks) is underway in the USA (NCT00632853).

At the present time, the results of our study indicate that four cycles of etoposide plus cisplatin plus concurrent AHTRT should continue to be the standard of care in patients with limited-stage SCLC. Because SCLC is strongly smoking-related, discouragement and cessation of tobacco use is still the most effective strategy to reduce deaths from SCLC.[23]

Contributors

TT was the chief investigator of the trial. KK, TH, SI, MN, MK, AY, FI, KT, SN, MH, HO, NY, TShin, HS, KM, KN, NS, and TT designed the trial and wrote the protocol. KK, TH, MN, MK, AY, FI, KT, SN, MH, HO, NY, TShin, HS, KM, KN, and TT enrolled patients. JM and TShib were responsible for data management, statistical analysis, and data interpretation. KK drafted the report. All authors were involved in writing the report and approved the final version.

Conflicts of interest

KK has received honoraria and a research grant from Daiichi-Sankyo. TT has received honoraria from Daiichi-Sankyo and Bristol-Myers Squibb. KN has received honoraria from Bristol-Myers Squib, Nippon Kayaku, and Daiichi-Sankyo. All other authors declare that they have no conflicts of interest.

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Original Study

A Randomized Phase III Study of Single-Agent Amrubicin Vs. Carboplatin/Etoposide in Elderly Patients With Extensive-Disease Small-Cell Lung Cancer

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Abstract

This study compared amrubicin monotherapy with carboplatin/etoposide combination therapy in elderly Japanese patients with extensive-disease small-cell lung cancer (ED-SCLC). The trial was prematurely closed owing to 3 treatment-related deaths in the amrubicin arm. Overall survival in the amrubicin and carboplatin/etoposide arms was 10.9 months and 11.3 months, respectively. Amrubicin monotherapy at 40 to 45 mg/m^2 was toxic and intolerable in elderly Japanese patients with ED-SCLC.

Introduction: The efficacy and safety of amrubicin, a third-generation synthetic anthracycline, were evaluated by comparison with carboplatin/etoposide combination therapy in elderly Japanese patients with extensive-disease small-cell lung cancer (ED-SCLC). **Patients and Methods:** Eligibility included histologically or cytologically proven SCLC, no previous systemic chemotherapy, performance status of 0 to 2, and age $\geq$ 70 years. Patients received amrubicin (70-74 years old, 40-45 mg/m^2; $\geq$ 75 years old, 40 mg/m^2) intravenously on days 1 to 3 every 3 weeks for 4 to 6 cycles or carboplatin (area under the curve of 5 intravenously on day 1) and etoposide (80 mg/m^2 intravenously on days 1 to 3) every 3 weeks for 4 to 6 cycles. **Results:** The target number of patients was 130 with 65 in each arm. However, the study was terminated early owing to 3 treatment-related deaths in the amrubicin arm, and only 62 patients (median age, 76 years; range, 70-88 years) were enrolled. The characteristics of the patients in the amrubicin and carboplatin/etoposide arms did not differ significantly. Overall survival, time to progression, and objective response rate were 10.9 vs. 11.3 months (P = .7353), 4.7 vs. 4.4 months, and 74.2% (23 of 31) vs. 60.0% (18 of 30), respectively, and quality of life showed no significant difference between the 2 arms. Higher incidences of febrile neutropenia and interstitial lung disease of grade 3 or worse occurred with amrubicin (34.4% vs. 3.3% and 12.5% vs. 0%, respectively). **Conclusion:** These results indicate that amrubicin monotherapy at 40 to 45 mg/m^2 is toxic and intolerable in elderly Japanese patients with ED-SCLC.

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Keywords: Chemotherapy, Interstitial lung disease, Pulmonary disease, Pulmonary toxicity, Treatment-related death

Introduction

Small-cell lung cancer (SCLC) has an extremely poor prognosis, despite initially being highly sensitive to chemotherapy and radiotherapy.[1,2] Approximately 30% to 40% of patients with SCLC are $\geq$ 70 years old at diagnosis.[3] Cases with extensive disease (ED) spreading beyond one hemithorax account for 60% to 70% of patients with SCLC. The standard therapy for ED-SCLC is systemic chemotherapy alone, which results in tumor shrinkage and

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symptom relief in 60% to 90% of cases, but most patients die of the disease within 2 years after diagnosis.[2] The standard regimen is a combination of cisplatin or carboplatin with etoposide. An objective tumor response rate of 73% and median overall survival of 10 months have been found in elderly patients with ED-SCLC who received these regimens.[4]

Amrubicin is a novel anthracycline derivative that has shown greater antitumor activity than doxorubicin against several human tumor xenografts implanted in nude mice.[5] A phase I study of amrubicin established a recommended dose for phase II studies of 45 mg/m^2/d for 3 consecutive days every 3 weeks.[6] A subsequent phase II study in previously untreated patients with ED-SCLC found an overall response rate of 76% and median survival of 11.7 months in 33 patients (age $\geq$ 70, 13; age $<$ 70, 20).[7] As second-line treatment, amrubicin gave a response rate of 44% to 53% and median survival of 9.3 to 11.6 months in patients with sensitive relapse and gave a response rate of 17% to 50% and median survival of 5.3 to 10.3 months in those with refractory relapse.[8-11] In these trials, hematologic toxicity, grade 3 to 4 neutropenia, febrile neutropenia, and thrombocytopenia occurred in 60% to 93%, 5% to 14%, and 20% to 40% of patients, respectively.

The objective of this study was to evaluate the efficacy and safety of amrubicin in comparison with carboplatin/etoposide combination therapy in elderly patients with ED-SCLC.

Patients and Methods

Study Design

This study was designed as a multicenter, randomized, nonblinded, phase III comparative study to test for noninferiority of amrubicin compared with carboplatin/etoposide in terms of survival. The primary endpoint was overall survival (OS), and the secondary endpoints were objective response rate, time to progression (TTP), and quality of life (QOL). The study was performed in accordance with the Declaration of Helsinki, the Japanese Pharmaceutical Affairs Law, and the International Conference on Harmonisation Good Clinical Practice guidelines. The protocol and informed consent form were approved by the institutional review board at each institution. Signed informed consent for participation was obtained from all patients. This study was registered at ClinicalTrials.gov (NCT00286169).

Patient Selection

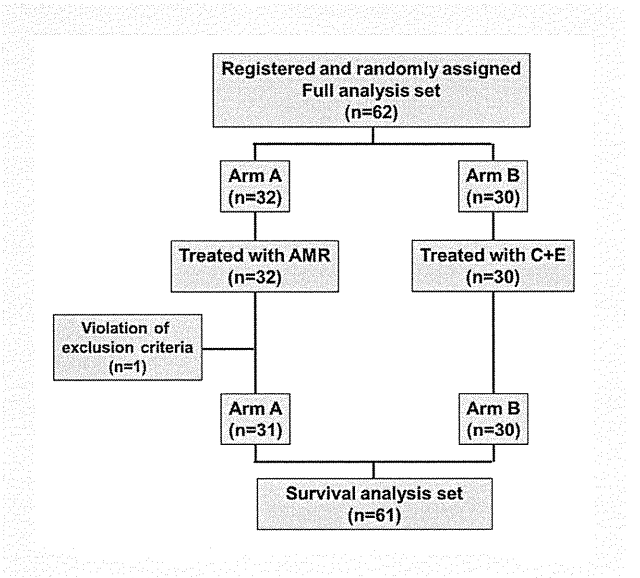
The eligibility criteria were histologically or cytologically proven SCLC; no previous chemotherapy; measurable disease; age $\geq$ 70 years; Eastern Cooperative Oncology Group performance status (PS) of 0 to 2; life expectancy of $\geq$ 2 months; adequate bone marrow function (white blood cell count of 4.0 $\times$ 10^9 to 12 $\times$ 10^9/L, neutrophil count $\geq$ 2.0 $\times$ 10^9/L, hemoglobin $\geq$ 9.5 g/dL, and platelet count $\geq$ 100 $\times$ 10^9/L); adequate liver function (aspartate aminotransferase and alanine aminotransferase $\leq$ 2.5 times the upper limit of the normal range and total bilirubin $\leq$ 1.5 mg/dL); adequate renal function (serum creatinine $\leq$ 1.5 mg/dL and glomerular filtration rate [GFR] calculated using the Cockcroft-Gault method $\geq$ 30 mL/min); adequate pulmonary function (PaO_2 $\geq$ 60 Torr under room air); adequate cardiac function (electrocardiogram without abnormal findings requiring treatment and left ventricular ejection fraction measured using echocardiography $\geq$ 60%); and written informed consent. Patients who received radiation or surgery for metastatic sites other than the primary site were eligible if they received these treatments 2 weeks or more before registration for this study.

Patients were excluded if they had symptomatic brain metastases; pleural or pericardial effusion or ascites that required drainage; superior vena cava syndrome; abnormal cardiac function that required treatment or a history of this condition; interstitial pneumonitis or lung fibrosis identified on chest radiograph; severe infection; serious syndrome of inappropriate secretion of antidiuretic hormone or uncontrolled diabetes mellitus; gastric or duodenal ulcer; or active prior malignancies with a disease-free interval of less than 5 years, except for carcinoma in situ. Pregnant or lactating women, men who had no intention of using contraception, and patients who had participated in registration-directed clinical trials in the previous 6 months were also ineligible.

Treatment Assignment and Drug Administration

The patients were randomly assigned to receive amrubicin monotherapy (arm A) or carboplatin/etoposide (arm B) by a prespecified minimization method of balancing the groups according to institution, age ($\geq$ 75 or $<$ 75 years), and PS (0-1 vs. 2). In arm A, amrubicin dissolved in 20 mL normal saline was administered once intravenously as a 5-minute infusion on days 1 to 3, every 3 weeks. At the start of the study, the dose of amrubicin was set at 45 mg/m^2/d for 3 days in patients aged $<$ 75 years and at 40 mg/m^2/d for 3 days in patients aged $\geq$ 75 years. However, 2 of the first 21 patients in arm A who received amrubicin at 45 mg/m^2/d died of severe infection associated with serious myelosuppression, and dose reduction was also required in subsequent cycles in 4 of 8 patients who started at 45 mg/m^2/d. In the amended protocol, the dose of

Figure 1 CONSORT Diagram. All Enrolled Patients (n = 62) Were Included as Participants for Treatment Delivery and Toxicity Analyses. One Patient in arm A was Excluded From the Efficacy Analysis Because of a Violation of Exclusion Criteria



Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide; CONSORT = Consolidated Standards of Reporting Trials.

amrubicin was set to 40 mg/m^2/d in all patients. In arm B, carboplatin was administered intravenously on day 1. The carboplatin dose was calculated using the Calvert formula, in which the target area under the curve (AUC) was 5 mg·min/mL. The GFR in the formula was calculated from the serum creatinine level using the Cockcroft-Gault method. Etoposide was administered intravenously at 80 mg/m^2 on days 1 to 3. In both arms, A and B, the chemotherapy was repeated every 3 weeks for a total of 4 to 6 cycles.

Toxicity Assessment and Treatment Modification

Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The criteria for dose reduction were common to both arms, as follows: grade 4 neutropenia lasting $\geq$ 4 days, febrile neutropenia, grade 4 thrombocytopenia, and grade 3 or severe nonhematologic toxicity, except for general malaise and hyponatremia. If any of these criteria occurred, the dose of amrubicin was reduced by 5 mg/m^2/d (arm A) or doses were reduced to a target AUC of 4 mg·min/mL for carboplatin and 60 mg/m^2/d for etoposide (arm B) in subsequent cycles.

QOL Evaluation

QOL was assessed using the Lung Cancer Subscale (LCS) of the Japanese version of the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire[12] and the Japanese version of the Euro-Qol 5-Dimension (EQ-5D) questionnaire.[13] QOL scores were obtained before chemotherapy, and 3 weeks (before the second cycle of chemotherapy), 3 months, 6 months, and 12 months after the start of chemotherapy.

Response Evaluation

Objective tumor response was evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0,[14] using CT or MRI for target and nontarget lesions performed every 4 weeks, and every 2 months after the best tumor response was established.

Poststudy Anticancer Treatments

After completion of the protocol-defined chemotherapy, no therapy for SCLC was allowed until disease progression or new lesions occurred (with progressive disease as defined in the RECIST criteria), except for prophylactic cranial irradiation in patients who achieved a complete response.

Statistical Analysis

OS and TTP were measured from the date of registration. Survival distributions were calculated by the Kaplan-Meier method and compared by the log-rank test. For OS, the point estimation and 95% confidence interval (CI) of the hazard ratio (HR) of arm A to arm B were calculated using a Cox proportional hazard model including age ($\geq$ 75 or $<$ 75 years old) and PS (0-1 vs. 2) as covariates. For the response rates in both arms, 95% CIs were calculated using methods for exact binomial CIs. A Fisher exact test was used for comparison of categorical data.

Noninferiority in OS would be obtained if the upper limit of a 2-sided 95% CI of the HR for OS was lower than 1.33. Based on previous studies, 1-year survival rates in arms A and B were assumed to be 48.5% and 36.0%, respectively. At a significance level of 5%,

Table 1 Patient Characteristics

	Arm A (n = 32) (AMR)		Arm B (n = 30) (C + E)		
	n	(%)	n	(%)	*P*
Sex					
Male	24	(75)	24	(80)	.764[a]
Female	8	(25)	6	(20)	
Age (years)					
71-74	14	(44)	13	(43)	1.000[a]
≥75	18	(56)	17	(57)	
Median (range)	76 (70-88)		75 (70-82)		.849[b]
PS					
0	5	(16)	7	(23)	.775[a]
1	20	(63)	17	(57)	
2	7	(22)	6	(20)	
Stage					
IIIB	6	(19)	1	(3)	.105[a]
IV	26	(81)	29	(97)	
Brain Metastasis					
No	27	(84)	22	(73)	.357
Yes	5	(16)	8	(27)	
LDH					
Median (range)	249 (144-1243)		376 (137-1081)		.0502

Abbreviations: AMR = amrubicin; C + E = carboplatin/etoposide; LDH = L-lactate dehydrogenase; PS = performance status.
[a]Fisher exact test.
[b]Wilcoxon rank-sum test.