A Phase II Study of Amrubicin and Topotecan Combination Therapy in Patients with Relapsed or Extensive-Disease Small-Cell Lung Cancer: Okayama Lung Cancer Study Group Trial 0401

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Running Title: Amrubicin and topotecan for SCLC

Conflict of Interest: none

UMIN clinical trial registry: C000000130

https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000000179&language=J

Abstract

Backgrounds: Chemotherapy is a mainstay in the treatment of extensive-disease small-cell lung cancer (ED-SCLC), although the survival benefit remains modest. We conducted a phase II trial of amrubicin (a topoisomerase II inhibitor) and topotecan (a topoisomerase I inhibitor) in chemotherapy-naïve and relapsed SCLC patients.

Methods: Amrubicin (35mg/m^2) and topotecan (0.75mg/m^2) were administered on days 3–5 and 1–5, respectively. The objective response rate (ORR) was set as the primary endpoint, which was assessed separately in chemotherapy-naïve and relapsed cases.

Results: Fifty-nine patients were enrolled (chemotherapy-naïve 31, relapsed 28). The ORRs were 74% and 43% in the chemotherapy-naïve and relapsed cases, respectively. Survival data were also promising, with a median progression-free survival time and median survival time of 5.3 and 14.9 months and 4.7 and 10.2 months in the chemotherapy-naïve and relapsed cases, respectively. Even refractory-relapsed cases responded to the treatment favorably (27% ORR). The primary toxicity was myelosuppression with grades 3 or 4 neutropenia in 97% of the patients, which led to grades 3 or 4 febrile neutropenia in 41% of the patients and two toxic deaths.

Conclusion: This phase II study showed the favorable efficacy and moderate safety profiles of a topotecan and amrubicin two-drug combination especially in relapsed patients with ED-SCLC.

Keywords: lung cancer, topotecan, amrubicin

1. Introduction

The standard regimen for patients with extensive disease small-cell lung cancer (ED-SCLC) has been cisplatin (CDDP)-based chemotherapy. Combination therapy with etoposide (ETP) and CDDP or irinotecan and CDDP has been very effective in previously untreated patients with ED-SCLC.[1,2] However, the long-term survival rate is low; early relapse occurs in the majority of responders, and salvage chemotherapy for SCLC yields disappointing results.[3] The survival of patients with ED-SCLC enrolled in phase III trials has not improved significantly over the last two decades, clearly suggesting the need for the further development of novel, more effective agents or combination regimens.[4]

Recently, several novel agents have been developed with unique mechanisms of action and have shown promise in the treatment of SCLC.[5] One of them, amrubicin, is an entirely synthetic anthracycline that inhibits DNA topoisomerase II activity. With an overall response rate (ORR) of 78.8% and median survival time (MST) of 11.0 months, amrubicin has demonstrated antitumor activity against previously untreated SCLC.[6] Another novel agent, topotecan, is a semi-synthetic water-soluble analog of camptothecin that inhibits DNA topoisomerase I activity. It, too, has shown favorable antitumor activity against SCLC with an ORR of 39% and MST of 9.0 months.[7] Previously, we conducted a phase I trial to determine the safety and efficacy of a two-drug combination chemotherapeutic regimen of amrubicin and topotecan in patients with untreated or relapsed ED-SCLC.[8]

Based on the results of the phase I trial, we conducted a phase II trial of amrubicin and topotecan in patients with untreated or relapsed ED-SCLC to determine

the ORR primarily. Secondary objectives were to investigate toxicity, progression-free survival (PFS), and overall survival.

2. Materials and methods

2.1. Eligibility criteria

Patients were recruited based on the following eligibility criteria: pathologically proven SCLC; chemotherapy-naïve ED-SCLC defined as distant metastasis, contralateral hilar lymph node metastasis or malignant pleural effusion,[9] or relapsed disease (one prior regimen allowed); Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 3; age ≤ 75 years; presence of measurable lesions; no chemotherapy within 4 weeks before entry in the study; adequate hematological [white blood cell (WBC) count ≥ 3000/μL, neutrophil count ≥ 1500/μL, hemoglobin level ≥ 8.5 g/dL, platelet count ≥ 10×10^4/μL], renal (serum creatinine level ≤ 1.5 mg/dL), and hepatic (total bilirubin level ≤ 1.5 mg/dL, serum transaminases ≤ 2.5 × upper limit of normal range) function; and adequate pulmonary reserves [arterial oxygen pressure (PaO_2) ≥ 60 Torr]. Relapsed cases included those with sensitive relapse (an interval of at least 90 days after the completion of first-line chemotherapy) and chemotherapy-refractory relapse (no response to first-line chemotherapy or relapse within 90 days after the completion of first-line chemotherapy). Patients with symptomatic brain metastasis, double cancer, massive effusion requiring drainage, or severe comorbidities (*e.g.*, uncontrolled diabetes, heart disease, infectious disease, or pulmonary fibrosis) were ineligible. Pretreatment evaluations included a complete history, physical examination, laboratory tests, chest radiography, electrocardiography, computed tomography (CT) of the chest and abdomen, magnetic resonance imaging

(MRI) of the brain, and a radionuclide bone scan. Staging was conducted according to the tumor, node, metastasis system.[10] Positron emission tomography (PET)/CT was also used for staging in some cases.

All patients gave written consent, and the protocol was approved by the institutional review board of each participating institute and performed in accordance with the amended 2000 version of the World Medical Association's Declaration of Helsinki.

2.2. Treatment scheme

The doses and schedules of both agents were based on phase I trial results.[8] Topotecan was diluted in 100 mL of physiological saline and administered intravenously as a 1-h infusion at a dose of 0.75 mg/m^2 on days 1 through 5. After completing the topotecan infusion, amrubicin was diluted in 20 mL of physiological saline and administered intravenously as a 5-min bolus injection at a dose of 35 mg/m^2 on days 3 through 5. Each patient was pre-medicated with intravenous dexamethasone and granisetron.

The treatment was repeated every four weeks for up to four cycles unless disease progression or unacceptable toxicity was observed, or the patient refused further treatment. Initiation of the next cycle of chemotherapy was delayed until the WBC and platelet count recovered to $\geq$ 3000/μL and $\geq$ 10 $\times$ 10^4/μL, respectively, and non-hematologic toxicities resolved to $\leq$ grade 1. Patients were permitted to receive any other chemotherapy for SCLC after completing or discontinuing the regimen. If hematological toxicity of grade 4 lasting more than 4 days or non-hematological toxicity $\geq$ grade 3 was observed in a prior cycle, the amrubicin dose was reduced each

cycle by 5 mg/m^2. The protocol treatment was stopped if patients developed the same toxicities after the second dose reduction. If grade 4 leukopenia, grade 4 neutropenia, or febrile neutropenia was observed, use of granulocyte colony-stimulating factor (G-CSF) was permitted.

2.3. Assessment of antitumor activity and toxicity

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 guidelines were applied to evaluate responses. Patients were evaluated for SCLC, with tumor assessments at baseline every two cycles, and at the end of treatment. The best overall response was defined as the best response recorded from the start of treatment until disease progression or recurrence. Complete and partial responses were confirmed by two observations no less than 4 weeks apart. A determination of stable disease required disease stabilization for at least 6 weeks. In this study, we also defined the disease control rate (DCR) as the proportion of patients with complete and partial responses and stable disease.[11] All toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. Patients were monitored closely for signs of cardiotoxicity during the study, and an electrocardiogram was required at the start of treatment.

2.4. Statistical Analysis

The primary endpoint of this study was the overall response rate (ORR), and secondary end points were PFS, overall survival, and the toxicity profile. The efficacy of topotecan and amrubicin combination therapy was assessed separately for chemotherapy-naïve and relapsed patients. For chemo-naïve cases, assuming that a 90%

ORR in eligible patients would indicate potential usefulness, whereas a 70% ORR would constitute the lower limit of interest, with $\alpha = 0.10$ and $\beta = 0.10$, the estimated accrual was 25 patients. For relapsed cases, assuming that a 30% ORR would indicate potential usefulness, whereas a 10% ORR would constitute the lower limit of interest, with $\alpha = 0.10$ and $\beta = 0.10$, the estimated accrual was also 25 patients. This regimen was to be rejected when < 12 and < 2 of the first 16 cases had an ORR at the interim analysis, for the chemotherapy-naïve and salvage cases, respectively. With an assumed 10% dropout rate, the number of patients needed was 28 each. Overall survival was defined as the interval between the date of enrollment in this study and death or the last follow-up visit. PFS was defined as the interval between the date of enrollment and the date of the first observation of disease progression or death from any cause. The survival distribution was estimated using the Kaplan-Meier method. All statistical analyses were conducted with STATA/SE version 10.0 software (College Station, TX).

3. Results

Patient characteristics and treatment delivery

A total of 59 consecutive patients with 31 chemotherapy-naïve or 28 relapsed ED-SCLC were enrolled from eight institutions. Their demographics are shown in Table 1. All patients were assessable for efficacy and safety. The median number of treatment cycles was four (range 1–7 cycles) and three (range 1–8 cycles) in the chemotherapy-naïve and relapsed cases, respectively. Among patients who received only three or less cycles of treatment, the most common reason for treatment cessation, was disease progression (15 of the 29 patients). At the time of analysis, 29 of 31 (94%) chemotherapy-naïve and 24 of 28 (86%) relapsed patients developed disease

progression. Of these, 26 chemotherapy-naïve and 11 relapsed patients received salvage chemotherapies: platinum-based doublet (n = 19), non-platinum-based doublet (n = 5), and monotherapy (n = 2) in the chemotherapy-naïve patients, and platinum-based doublet (n = 4), non-platinum doublet (n = 1), and monotherapy (n = 6) in the relapsed patients.

Response

Due to early febrile neutropenia-related death (day 20, cycle 1), one patient received no formal response assessment. The planned interim analysis revealed this regimen had potent activity (13 and 6 responders) and the committee decided to continue further patient accrual in the chemotherapy-naïve and salvage settings, respectively. The ORR of chemotherapy-naïve patients was 74% (95% confidence interval (CI) 55–88%). This did not satisfy the initial setting of the lower limit of interest (70%), and thus the primary endpoint was not met for this population. By contrast, 43% of relapsed patients responded to the study treatment (95% CI 24–63%), which clearly met the lower limit of interest (10%).

In 28 relapsed patients, the ORR and DCR were 53% and 82%, respectively, for the sensitive-relapsed cases, and 27% and 82%, respectively, for the refractory-relapsed cases (Table 2).

Survival

All the patients were assessable for the survival analysis. At the time of this analysis (January, 2010), 11 patients were still alive, and median follow-up time was 43.2 months ranging from 4.3 to 75.9 months. The median PFS time was 5.3 months for

198 the chemotherapy-naïve cases and 4.7 months for relapsed cases (Table 3 and Figure 1).
199 The overall median survival time (MST) was 14.9 and 10.2 months for the
200 chemotherapy-naïve and relapsed cases, respectively. When relapsed cases were
201 classified by the type of relapse pattern, the median progression-free survival was 5.8
202 months in patients with sensitive relapse and 3.3 months in patients with refractory
203 relapse. The overall median survival time was 10.2 and 10.5 months in sensitive and
204 refractory relapse, respectively (Figure 2).
205
206 *Safety*
207 Adverse events of grade 3 or worse are listed in Table 4. Myelosuppression was
208 the primary adverse event. Grades 3 and 4 neutropenia, thrombocytopenia, and anemia
209 were observed in 97%, 51%, and 42% of the patients, respectively. Median duration of
210 neutropenia was five days. G-CSF was administered in 50 patients (85%), whereas 14
211 patients received blood transfusion. Grade 3 or worse non-hematological toxicities
212 including anthracycline-related cardiac toxicities were relatively mild, except for febrile
213 neutropenia, which resulted in two treatment-related deaths (chemo-naïve setting and
214 refractory relapsed setting in one each).
215
216 **4. Discussion**
217 In this relatively small study, the combination of amrubicin and topotecan
218 yielded an ORR of 74% and 43% in the chemotherapy-naïve and relapsed cases,
219 respectively. The survival data were also promising with a median PFS time and MST
220 of 5.3 and 14.9 months and 4.7 and 10.2 months in the chemotherapy-naïve and
221 relapsed cases, respectively. Even refractory-relapsed cases responded to this treatment

(27% ORR). The major observed toxicity was myelosuppression. Grades 3 and 4 neutropenia occurred in 97% of the patients, resulting in grades 3 and 4 febrile neutropenia in 41% of the patients.

In a first-line setting, platinum plus irinotecan or etoposide is considered a standard treatment for ED-SCLC and approved in Japan. These regimens produce an ORR of 68 to 84%, a median PFS of 4.8 to 6.9 months, and a MST of 9.4 to 12.8 months.[1] Combination therapy consisting of cisplatin plus topotecan or cisplatin plus amrubicin has also been evaluated and has similar effects (56 to 88% ORR, 7.0-month median PFS, and 10.3 to 13.6 month-MST.[12,13] In this study, combination therapy of topotecan and amrubicin produced less favorable efficacy than we initially expected although it yielded a nearly identical efficacy with a 74% ORR, 5.3-month median PFS, and 14.9 month-MST.

With regard to relapsed patients, Inoue *et al*. conducted a randomized phase II trial of amrubicin versus topotecan for relapsed SCLC patients and reported an ORR of 38% and 13% in amrubicin monotherapy and topotecan monotherapy, respectively.[14] The respective median PFS times and MSTs were 3.5 and 8.1 months (amrubicin monotherapy) and 2.2 and 8.4 months (topotecan monotherapy). Based on our *post-hoc* sub-analysis stratifying relapse type, the efficacy of the amrubicin and topotecan combination therapy seemed more favorable especially in the refractory-relapsed cases when compared simply with each single therapy (27% vs. 0–17% ORR, 82% vs. 18–68% DCR, 3.3 vs. 1.5–2.6-month median PFS, and 10.5 vs. 5.3-5.4-month MST).[14] Another trial also showed somewhat lower response rate of amrubicin monotherapy for refractory cases.[15] This might suggest some synergistic effects of the two drugs despite the need for further investigations.

As for the toxicity profiles, neutropenia in our combination therapy was mainly moderate, which parallels that in our prior phase I trial.[8] The occurrence of neutropenia in 83-93% of the patients undergoing amrubicin monotherapy[14,16,17] and 87% of the patients undergoing topotecan monotherapy[14] seemed also similar to our findings. Furthermore, as in monotherapy, non-hematological toxicities other than febrile neutropenia of the amrubicin and topotecan combination therapy were generally tolerable. However, thrombocytopenia, anemia, febrile neutropenia and two toxic deaths seemed more severe in the combination therapy than the monotherapy[6,14,15], suggesting the need for cautious administration of the doublet therapy.

We have several limitations. Since this was an exploratory phase II single-arm trial, some selection bias is possible, and a simple comparison between our results and historical clinical data would be unwarranted and inconclusive. A prospective comparative study is clearly required. Also, this study design mixes up 3 populations of patients (untreated, relapsed-sensitive, and relapsed-refractory). Since only 59 patients enrolled, interpretation of the results is limited by the 3 small subsets of patients. The two populations of relapsed patients should have been stratified prospectively. Furthermore, we accrued PS3 patients as well as PS 0-2 patients in this study according to the previous clinical trial designs[18,19]. However, to date, this inclusion criterion has been unusual in most clinical trials, and the great majority of patients accrued in this study had indeed an excellent PS (0 or 1 in 93%). Thus, the efficacy and safety for PS 2-3 pts would still remain unclear.

5. Conclusions

In conclusion, this phase II study showed the favorable efficacy and moderate safety profiles of a topotecan and amrubicin two-drug combination especially in relapsed patients with ED-SCLC, while this regimen was less effective in the first-line setting and not worth while further being evaluated.

Conflict of Interest

None declared.

Acknowledgment

We thank the Okayama Lung Cancer Study Group members for their dedication and cooperation throughout the course of this work. The authors are also deeply grateful for all of the participants who made this study possible.

Contributors

KH, KK, and HU were involved in the conception and design of the study. NN, KH, SK, KK, NT, KC, TS, DK, SH, AT, SH, and MTwere involved in the provision of study material, patients, and data acquisition. KH, KK and NT were involved in data analysis and interpretation. All authors were involved in writing the report and approved the final version.

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All table & figure captions

Table 1 Demographics of the patients (n = 59)

Table 2 Subset analysis of efficacy stratified by the type of relapse

Table 3 Objective response and survival

Table 4 Adverse events (grade 3 or worse)

Figure 1. Overall (solid) and progression-free (dotted) survival curves
A, chemotherapy-naïve patients; B, relapsed patients

Figure 2. Overall (solid) and progression-free (dotted) survival curves
A, sensitive-relapsed patients; B, refractory-relapsed patients

Table 1 Demographics of the patients (n = 59)

	Chemo-naïve (n=31)	Relapsed (n=28)
Age, median (range), years	67 (52-75)	69 (54-73)
Gender (M / F)	28 / 3	24 / 4
ECOG PS (0 / 1 / 2)	3 / 26 / 2	11 / 15 / 2
Smoking history	11 / 15 / 2	16 / 12 / 3
(current / former / never)		
Prior irinotecan use	-	7
Prior etoposide use	-	21
Type of treatment setting		
sensitive relapse	-	17
refractory relapse	-	11

Sensitive relapse (at ≥ 90 days after completion of first-line chemotherapy).
Chemotherapy-refractory relapse (no response to first-line chemotherapy or relapse within 90 days after completing first-line chemotherapy). Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status.

Table 2 Subset analysis of efficacy stratified by the type of relapse

	Sensitive relapse (n=17)		Refractory relapse (n=11)	
Response	No.	%	No.	%
complete response	0	0	0	0
partial response	9	53	3	27
stable disease	5	29	6	55
progressive disease	2	12	2	18
inevaluable	1*	6	-	-
Overall response rate	9	53	3	27
Disease control rate	14	82	9	82
Survival				
median PFS (months)	5.8		3.3	
median OS (months)	10.2		10.5	
1-yr OS (95%CI; %)	38.2 (15.9–60.5)		18.2 (2.9–44.2)	

**Early death. Abbreviations: PFS = progression-free survival, OS = overall survival, CI = confidence interval.

Table 3 Objective response and survival

	Chemo-naïve (n=31)		Relapsed (n=28)	
Response	No.	%	No.	%
complete response	1	3	0	0
partial response	22	71	12	43
stable disease	6	19	11	39
progressive disease	2	6	4	14
inevaluable	-	-	1*	3
Overall response rate	23	74	12	43
(95% CI)		(55 to 88)		(24 to 63)
Disease control rate	29	94	23	82
Survival				
median PFS (months)	5.3		4.7	
median OS (months)	14.9		10.2	
1-yr OS (95% CI; %)	68.4 (47.8–82.3)		29.9 (14.3–47.4)	

*Early death. Abbreviations: PFS = progression-free survival, OS = overall survival, CI = confidence interval.

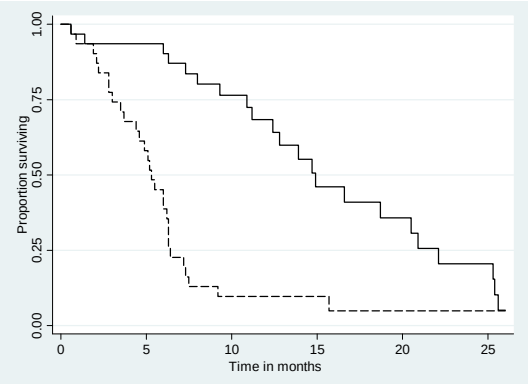
15 Table 4 Adverse events (grade 3 or worse)

	Grade 3	Grade 4	≥Grade 3(%)
Hematologic			
neutropenia	10	47	97
thrombocytopenia	15	15	51
anemia	21	4	42
Non-hematologic			
fatigue	2	3	9
febrile neutropenia	20	4	41
nausea/vomiting	2	1	5
diarrhea	0	1	2
pneumonitis	1	1	3
ileus	0	1	2

16

Figure 1

A B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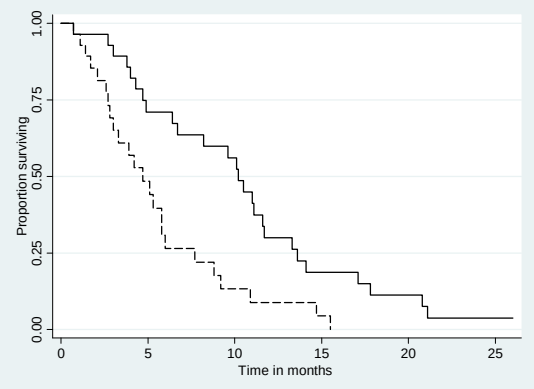
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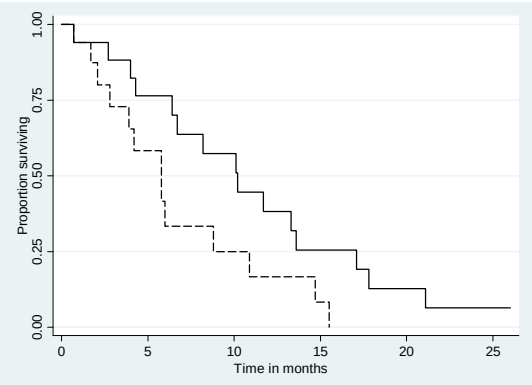
Figure 2

A B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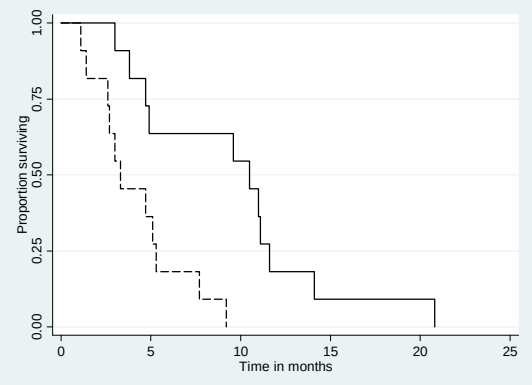
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