厚生労働科学研究費補助金
がん臨床研究事業

再発小細胞肺癌に対する標準的治療法の確立に関する研究

平成25年度　総括研究報告書

研究代表者　後藤　功一

平成26（2014）年　4月

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Ⅰ．総括研究報告

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再発小細胞肺癌に対する標準的治療法の確立に関する研究

研究代表者　後藤　功一
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研究要旨

再発小細胞肺がんに対する標準治療の確立を目的に、標準治療と見なされているノギテカン(NGT)療法に対して、我が国で新しく開発されたシスプラチン＋エトポシド＋イリノテカン(PEI)療法の優越性を多施設共同第III相比較試験において検証する。本臨床試験は、平成19年8月Japan Clinical Oncology Group (JCOG)プロトコール審査委員会の承認を経て、平成19年9月20日より開始となり、参加各施設における倫理審査委員会の承認を経て、平成20年1月より本格的に症例登録が始まった。症例集積ペースが予定よりもやや遅かったが、当初の集積期間4年間より約1年間遅れて、平成24年11月19日に180例の予定症例集積が完了した。平成26年3月でイベント（死亡例）が154例となり、目標イベント151例に到達したため、最終解析を行い、結果を学会等で公表する予定である。

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A.　研究目的

再発小細胞肺がん（初回治療が奏効して、治療終了から90日以上経過して再発を認めたsensitive relapse）を対象にして、現在の標準的治療法と見なされるノギテカン(NGT)療法に対するシスプラチン＋エトポシド＋イリノテカン療法(PEI療法)の優越性を検証すること

を目的とする。

B. 研究方法

全国40施設の研究グループによる多施設共同第 III 相比較試験で、エンドポイントは生存期間である。生存期間中央値（MST）を8ヶ月から12ヶ月に向上させることを見込んでいる。

対象患者は、再発小細胞肺がん（初回治療が奏効して、治療終了から90日以上経過して再発を認めたsensitive relapse）であり、小細胞肺がんに対する外科的切除術の既往がなく、初回治療としてプラチナ製剤を含む併用化学療法または放射線化学療法を受けており、75 才以下、ECOG Performance Status (PS) 0-2、主要臓器機能が保持されており、患者本人の自由意思による文書同意が得られた患者である。

JCOG データーセンターでの中央登録、無作為化割り付けを行う。なお、割付調整因子は、PS、再発時病期、施設である。

治療内容は、NGT 療法、あるいは PEI 療法を行う。NGT 療法は、ノギテカン 1.0 mg/m^2(day1-5)、3 週間隔、4 コースとする。PEI 療法は、第 1 週目：シスプラチン(25 mg/m^2, day 1)＋エトポシド(60 mg/m^2, day 1-3)、第 2 週目：シスプラチン(25 mg/m^2, day 1)＋イリノテカン(90 mg/m^2, day 1)の 2 週間を 1 コースとして 5 コース(計 10 週）の治療法である。PEI 療法は、1 コース目の第 8 日目より G-CSF を抗癌剤投与日以外に連日投与する。

中間解析は 1 回、安全性モニタリングは原則年 2 回。予定症例数は 180 例で、症例集積期間は当初は 4 年間の予定であったが、症例集積ペースが遅いため、6 年間に延長した。最新のモニタリングレポートにおいて、全患者の MST が 16 ヶ月であり、研究計画時に想定された 10 ヶ月よりもかなり良好なため、最終解析は、症例集積終了後 1 年から 2 年へ延長した。

(倫理面への配慮)

参加患者の安全性確保については、適格条件やプロトコール治療の中止変更規準を厳しく設けており、試験参加による不利益は最小化される。また、「臨床研究に関する倫理指針」およびヘルシンキ宣言などの国際的倫理原則に従い以下を遵守する。

1) 研究実施計画書の IRB 承認が得られた施設のみから患者登録を行う。

2) すべての患者に登録前に充分な説明と理解に基づく自発的同意を本人より文書で得る。

3) データの取り扱い上、直接個人が識別できる情報を用いず、かつデータベースのセキュリティを確保し、個人情報の保護を厳守する。

4) JCOG のプロトコール審査委員会、効果・安全性評価委員会、監査委員会、放射線治療委員会などによる第三者的監視を受けることを通じて、科学性と倫理性の確保に努める。

C. 研究結果

全国の肺がん臨床研究の主要 40 施設で研究グループを組織し、平成 19 年 9 月 20 日より本試験を開始した。症例集積ペースが予定よりもやや遅かったため、登録期間を 2 年間延長した結果、平成 24 年 11 月 19 日に目標症例数である 180 例の登録が完了した。平成 22 年 9 月に行われた JCOG 効果・安全性評価委員会の中間解析審査においても本試験の継続が認められており、当初の予定より 1 年遅れて約 5 年間で症例集積が完了した。平成 26 年 3 月でイベント（死亡例）が 154 例となり、目標イベント 151 例に到達したため、最終解析を行い、6 月の米国臨床腫瘍学会で最終結果を報告する予定である。

平成 26 年度後期定期モニタリングレポートによる 180 例の解析では、NGT 療法と PEI 療法それぞれにおけるグレード 3 以上の好中球減少 85.6% vs. 83.3%、ヘモグロビン減少 27.8% vs. 84.4%、血小板減少 27.8% vs. 41.1%、下痢 0% vs. 7.8%、発熱性好中球減少 6.7% vs. 31.1%であり、毒性は明らかに PEI 療法が強かった。治療関連死亡は NGT 群で 2 例、PEI 療法で 1 例認めた。一方、平成 26 年 2 月 20 日現在の両群合わせた 180 例の MST は 15.5 ヶ月であり、現時点で両群の差を知ることは出来ないが、高い治療効果が期待される。

D. 考察

小細胞肺がんは全肺がんの 10-15%を占め、非小細胞肺がんに比べると化学療法や放射線療法の感受性が高く、初回治療に対する奏効率は限局型で 80-100%, 進展型で 60-80%である。しかし、80-90%の小細胞肺がんは再発を来し、5 年生存率は限局型で約 25%、進展型で 0-5%であり、小細胞がん全体の 5 年生存率は 10%未満と不良である。再発後の化学療法に対する反応は悪く、再発から死亡までの MST は 3-4 ヶ月と言われて来た。

近年、再発小細胞肺がんは、初回化学療法が奏効し、治療終了から 60-90 日以上経過して再発を認める sensitive relapse と、初回治療が奏効しない、あるいは奏効しても 60-90 日以内に再発を認める refractory relapse の 2 つに分類されて、臨床研究が行われてきた。これは、

この 2 群で化学療法の効果や生存期間に差を認めるためである。例えば、NGT 療法でみると、奏効率、MST は、sensitive relapse では 14-37%、25-37 週、refractory relapse では 6-11%、16-20 週である。

現在までに再発小細胞肺がん(sensitive relapse)を対象とした 4 つの大規模な第 III 相試験が報告されている。NGT 療法とシクロホスファミド+アドリアマイシン+ビンクリスチン(CAV)療法を比較した第 III 相試験では、MST:25.0 週対 24.7 週と有意差を認めなかったが、再発に伴う症状の改善では NGT 療法が優れていた。NGT 療法の経口投与法と静脈投与法の比較試験では、奏効率、生存に有意差を認めず、毒性も同程度であった。また、NGT 療法の経口投与と無治療の第 III 相試験では、NGT 療法の有意な MST の延長(26 週対 14 週)を認めた。2011 米国臨床腫瘍学会(ASCO)では、NGT 療法とアムルビシン療法の第 III 相試験の結果が報告されたが、生存に有意差を認めなかった。再発小細胞肺がんに対する標準的化学療法は確立していないが、上記 4 つの第 III 相試験の結果に基づいて、世界的に NGT 療法が再発小細胞肺がんに対する標準治療とみなされている。そこで、再発小細胞肺癌(sensitive relapse)に対する標準治療の確立を目指して、 NGT 療法と我々が開発した PEI 療法の第 III 相比較試験を実施した。平成 26 年 3 月で目標イベント数に到達したため、最終解析を行い、最終結果を公表する予定である。

E. 結論

「再発小細胞肺癌に対する標準的治療法の確立に関する研究」では、「再発小細胞肺癌に対する NGT 療法と PEI 療法を比較する第 III 相試験(JCOG0605)」を平成 19 年 9 月 20 日より多施設共同試験として開始し、平成 24 年 11 月 19 日に 180 例の予定症例集積が完了した。平成 26 年 3 月で目標イベント数に到達したため、最終解析を行い、最終結果を公表する予定である。

F. 健康危険情報

厚生労働省に報告した健康危険情報なし。

G. 研究発表

1. 論文発表.

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H. 知的財産権の出願・登録状況

1. 特許取得
   なし
2. 実用新案登録
   なし
3. その他
   なし

Ⅱ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Ⅲ. 研究成果の刊行物・別刷

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A single-arm confirmatory study of amrubicin therapy in patients with refractory small-cell lung cancer: Japan Clinical Oncology Group Study (JCOG0901)☆

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ABSTRACT

Objectives: We conducted an open-label, multicenter, single-arm study to confirm the efficacy and safety of amrubicin (AMR), a topoisomerase II inhibitor, for treating refractory small-cell lung cancer (SCLC).
Patients and methods: Patients with chemotherapy-refractory SCLC received 40 mg/m^2 AMR for 3 consecutive days, every 21 days. The primary endpoint was the overall response rate (ORR) and the secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety.
Results: Between November 2009 and February 2011, 82 patients were enrolled. Each patient received a median of four treatment cycles (range, 1–22 cycles). ORR was 32.9% [$P < 0.0001$ by the exact binomial test for the null hypothesis that ORR $\leq$ 10%; 95% confidence interval (CI), 22.9–44.2%]. The median PFS and OS periods were 3.5 months (95% CI, 3.0–4.3 months) and 8.9 months (95% CI, 7.6–11.3 months), respectively. Significant differences in ORR (21.4% *v* 45.0%; $P = 0.034$), PFS (median, 2.9 *v* 5.1 months; $P = 0.0009$), and OS (median, 7.9 *v* 13.1 months; $P = 0.0128$) were observed between patients previously treated with etoposide and others. Neutropenia was the most common grade 3 or 4 adverse events (93.9%), and febrile neutropenia developed in 26.8% patients. No treatment-related death occurred.
Conclusions: AMR monotherapy can be considered an effective and safe treatment option for refractory SCLC. Previous chemotherapy with etoposide may influence AMR efficacy.

1. Introduction

Small-cell lung cancer (SCLC) is the most rapidly growing lung cancer subtype and patient prognosis is extremely poor [1]. Although most SCLC patients respond to initial treatment, long-term survival is low. Unfortunately, disease progression or relapse occurs in almost all advanced-stage SCLC patients and in the majority of early-stage SCLC patients [2–6]. Response to subsequent chemotherapy depends on responsiveness to previous induction

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chemotherapy and the interval between cessation of initial therapy and disease progression [7,8].

Overall response rates (ORRs) of 21–38% and median overall survival (OS) of 6.9–11.7 months were reported in chemotherapy-sensitive SCLC patients after treatment with topotecan, a topoisomerase I inhibitor [8,9]. A previous randomized study demonstrated similar efficacy and improved tolerability of topotecan compared with cyclophosphamide, doxorubicin, and vincristine [10]. Topotecan is also considered as a treatment option for chemotherapy-refractory SCLC; however, low ORRs (0–11%) and OS (median, 4.7–5.4 months) have been reported [8,9,11]. Thus, a standard chemotherapy for the treatment of refractory SCLC has not yet been established. However, effective treatment must be developed to improve prognosis for SCLC patients.

Amrubicin (AMR), a fully synthetic 9-aminoanthracycline, is metabolized in the body to the active metabolite amrubicinol, which has higher antitumor activity than AMR. Both AMR and amrubicinol, which are topoisomerase II inhibitors, exhibit antitumor activities against various human tumors in xenograft models and have shown no risk of typical anthracycline cardiotoxicity [12]. In subgroup analyses of small phase II studies, AMR showed promising activity in patients with refractory SCLC with ORR of 17–50% and median OS of 5.3–10.3 months [9,13].

Accordingly, the results of previous studies indicated that AMR may be useful for treating refractory SCLC. Therefore, we conducted this study to confirm the efficacy and safety of AMR, a topoisomerase II inhibitor, for treating refractory SCLC. A phase III trial was preferred to evaluate the effectiveness of AMR therapy; however, other than AMR therapy, there was no promising treatment under development for refractory SCLC at that time. As second-best evidence that was not from a randomized controlled trial, we designed a nonrandomized single-arm confirmatory study to evaluate whether AMR therapy can be considered as a standard treatment for refractory SCLC.

2. Patients and methods

2.1. Study design

This was an open-label, multicenter, single-arm confirmatory study involving 25 institutions in Japan. The study protocol was approved by the Japan Clinical Oncology Group (JCOG) Protocol Review Committee and the institutional review board of each participating institution.

2.2. Eligibility criteria

Patients were required to have histologically or cytologically documented SCLC, and were refractory to treatment with one or two previous chemotherapy regimens, at least one of which was platinum based. Refractory disease was defined as no response to previous chemotherapy, disease progression on chemotherapy, or disease progression <90 days of completing previous chemotherapy after confirming a complete response (CR) or partial response (PR). Other inclusion criteria included age of 20–74 years, Eastern Cooperative Oncology Group performance status of 0–1, measurable disease, no history of chemotherapy with AMR, no history of surgery for SCLC, no thoracic radiation therapy ≤4 weeks before registration, adequate baseline organ function [leukocyte count ≥ 3000/mm^3, absolute neutrophil count ≥ 1500/mm^3, hemoglobin ≥ 9.0 g/dL, platelet count ≥ 100,000/mm^3, total bilirubin ≤ 2.0 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 100 IU/L, serum creatinine level ≤ 2.0 mg/dL, PaO_2 under room air ≥ 60 mmHg, and electrocardiographic findings within normal range]. Written informed consent was obtained from all patients. Patients were ineligible if they had active concomitant malignancy, massive pleural or pericardial effusion, symptomatic brain metastasis, or severe comorbidities such as active infections, uncontrolled hypertension, severe heart disease, uncontrolled diabetes mellitus, bowel obstruction, psychiatric disease, severe emphysema, interstitial pneumonia, or pulmonary fibrosis. Patients having systemic steroid medication and pregnant or breast feeding women were also excluded.

2.3. Treatment

Treatment was started within 1 week after enrollment in the study. Patients received AMR at 40 mg/m^2/day for 3 consecutive days, every 21 days. The treatment was repeated until disease progression, intolerable toxicity, or patient refusal. The dose of AMR was decreased to 35 mg/m^2/day if any of the following were observed during the previous course: leukocyte count <1000/mm^3, platelet count <20,000/mm^3, grade 3 febrile neutropenia, or grade 3 nonhematological toxicity (except nausea, anorexia, weight loss, creatinine, hyponatremia, hyperglycemia or alopecia). A second dose reduction to 30 mg/m^2/day was made in subsequent cycles on the basis of the same criteria. In cases of grade 4 nonhematological toxicity or continued toxicity that would have required a third dose reduction, the protocol treatment was terminated.

Patients received full supportive care as required, including transfusion of blood products. The protocol specified that granulocyte colony-stimulating factor (G-CSF) should be used in accordance with the national health insurance coverage of Japan, indications for G-CSF administration were as follows: (a) when fever (in principal over 38 °C) was observed with a neutrophil count of ≤1000/mm^3; (b) when a neutrophil count of 500/mm^3 was observed; (c) during the previous course, if fever (in principal over 38 °C) with a neutrophil count of ≤1000/mm^3 was observed, or if a neutrophil count of 500/mm^3 was observed, then after completing the same chemotherapy, if a neutrophil count of ≤1000/mm^3 was observed. There was no restriction for subsequent chemotherapy after disease progression in this study.

2.4. Evaluation

The Response Evaluation Criteria in Solid Tumors guidelines (ver. 1.0) was used to evaluate tumor response [14]. Computed tomography was performed at baseline and at least every two cycles. Confirmation of a CR or PR was required at least 4 weeks after the first documentation of a response. Independent review of tumor response was performed for patients with any extent of tumor shrinkage. Three reviewers, including a diagnostic radiologist, were assigned as an independent review panel. Adverse events were recorded and graded using the Common Terminology Criteria for Adverse Events (ver. 3.0). Evaluation of cardiotoxicity was performed as needed, as judged by the physician.

2.5. Study endpoints and statistical analysis

The primary endpoint in this study was ORR, which was calculated as confirmed response (CR + PR) according to independent assessments. We believe that tumor shrinkage is essential to improve prognosis for refractory SCLC. Furthermore, previous studies for refractory SCLC showed large variations in survival times [8,9,11,13]. Because ORR with slight variation was considered a hard endpoint, we used ORR as the primary endpoint. As secondary endpoints, we evaluated progression-free survival (PFS) and OS as effectiveness endpoints and the incidence of an adverse event as a safety endpoint. We hypothesized that if the ORR of AMR therapy was high enough compared with that of topotecan therapy, AMR

could be considered as a standard treatment option. The sample size was set as $N = 80$ to achieve a power of at least 80% with a one-sided alpha of 0.05, and expected and threshold values for the primary endpoint of 20% and 10%, respectively. Survival was estimated using the Kaplan–Meier method and subgroups were compared using the log-rank test.

For AMR therapy to be considered as a standard option for patients with refractory SCLC, its safety and survival should also be equal or superior to those of topotecan therapy. According to the results of previous topotecan studies [8,9,11], anticipated values were 2.0–3.0 months for median PFS and 5.0–7.5 months for median OS, and a proportion of treatment-related deaths (≤5%) was also anticipated. The Fisher's exact test was used to compare categorical data. All analyses were performed using SAS release 9.1 statistical software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient characteristics

From November 2009 to February 2011, a total of 82 patients (17 women and 65 men; median age, 66 years; age range, 44–74 years) from 25 Japanese institutions were enrolled in this study. All 82 patients were eligible for analysis of the efficacy and safety of AMR. Patient characteristics are listed in Table 1. All 82 patients received prior platinum-based chemotherapy, including pretreatment with irinotecan-containing chemotherapy regimens ($n = 47$, 57.3%) and etoposide-containing chemotherapy regimens ($n = 42$, 51.2%). Thirteen of these patients had received thoracic radiation therapy concurrently or sequentially with chemotherapy.

Each patient received a median of four AMR treatment cycles (range, 1–22 cycles), and 18 (22.0%) had a cumulative AMR doses exceeding 750 mg/m^2. Reasons for off-protocol included disease progression ($n = 67$), unacceptable toxicity ($n = 8$), and patient refusal possibly related to adverse events ($n = 7$). AMR dose reduction was required in 31 patients (37.8%), and the dose was decreased by two levels in seven patients (8.5%).

Table 1
Patient characteristics ($N = 82$).

Characteristics	Patients	
	n	%
Age (years)		
Median	66	
Range	44–74	
Gender		
Female	17	20.7
Male	65	79.3
ECOG performance status		
0	34	41.5
1	48	58.5
Disease extent at entry		
Limited disease	6	7.3
Extensive disease	76	92.7
No. of prior chemotherapy regimens		
1	72	87.8
2	10	12.2
Prior chemotherapy regimen (multiple choices)		
Cisplatin-containing	62	75.6
Carboplatin-containing	26	31.7
Cisplatin and carboplatin-containing	6	7.3
Irinotecan-containing	47	57.3
Etoposide-containing	42	51.2
Topotecan-containing	3	3.7
Response to prior chemotherapy		
Complete response	3	3.7
Partial response	58	70.7
Stable disease	4	4.9
Progressive disease	17	20.7
History of thoracic radiation therapy		
No	69	84.1
Yes	13	15.9

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2
Response to amrubicin in the intent-to-treat population.

Response	Number of patients	%
CR	2	2.4
PR	25	30.5
SD	37	45.1
PD	16	19.5
Not evaluable	2	2.4
Overall response rate (CR + PR)	27	32.9
95% CI[a]		22.9–44.2

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.
[a] Calculated by the exact method.

3.2. Response

Independent reviews of tumor response were performed for 39 patients with any extent of tumor shrinkage. Among the total study population, CR was achieved in two patients (2.4%), PR in 25 (30.5%), stable disease (SD) in 37 (45.1%) after two courses, and progressive disease (PD) in 16 (19.5%). The response was not evaluable in two patients (2.4%) as a result of early termination of the treatment protocol. One patient refused further treatment after one cycle of AMR therapy, and the other terminated therapy because of poor performance status. Thus, for AMR therapy, an ORR of 32.9% was observed in our study population ($P < 0.0001$ by the exact binomial test for the null hypothesis that ORR ≤10%; 95% CI, 22.9–44.2%) (Table 2).

In a subset analysis of response to AMR, ORR was lower in patients treated with etoposide than in others (21.4% *v* 45.0%, respectively; $P = 0.034$) (Table 3). No remarkable difference in ORR was observed according to demographic characteristics [age,

Table 3
Subset analysis of response to amrubicin.

Characteristics	Number of patients	Response rate (%)	*P*
Age (years)			
44–70	61	32.8	1.00
≥71	21	33.3	
Gender			
Female	17	47.1	0.25
Male	65	29.2	
ECOG performance status			
0	34	35.3	0.81
1	48	31.3	
Disease extent at entry			
Limited disease	6	16.7	0.66
Extensive disease	76	34.2	
No. of prior chemotherapy regimens			
1	72	36.1	0.15
2	10	10.0	
Prior treatment with irinotecan			
No	35	25.7	0.25
Yes	47	38.3	
Prior treatment with etoposide			
No	40	45.0	0.034
Yes	42	21.4	
Response to prior chemotherapy			
CR/PR	61	36.1	0.42
SD/PD	21	23.8	
History of thoracic radiation therapy			
No	69	33.3	1.00
Yes	13	30.8	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, stable disease; PD progressive disease.

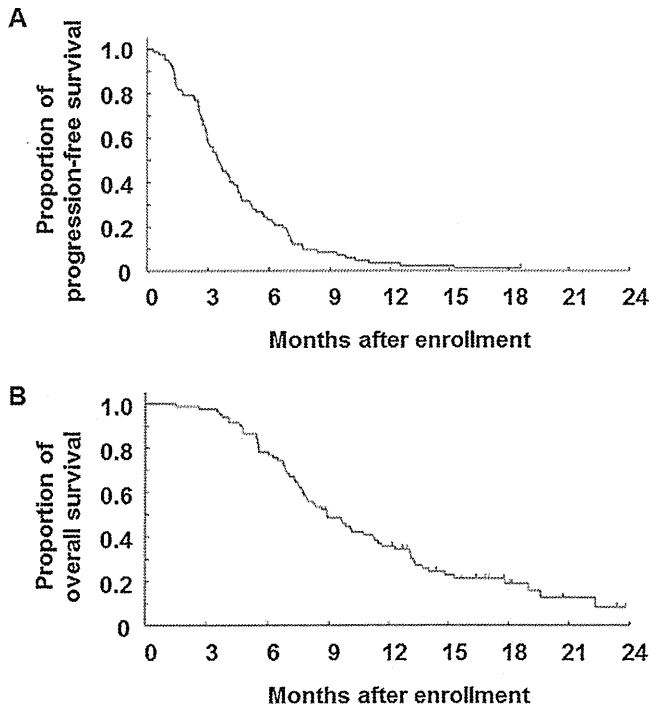

Fig. 1. (A) Progression-free survival and (B) overall survival of patients treated with amrubicin ($n = 82$).

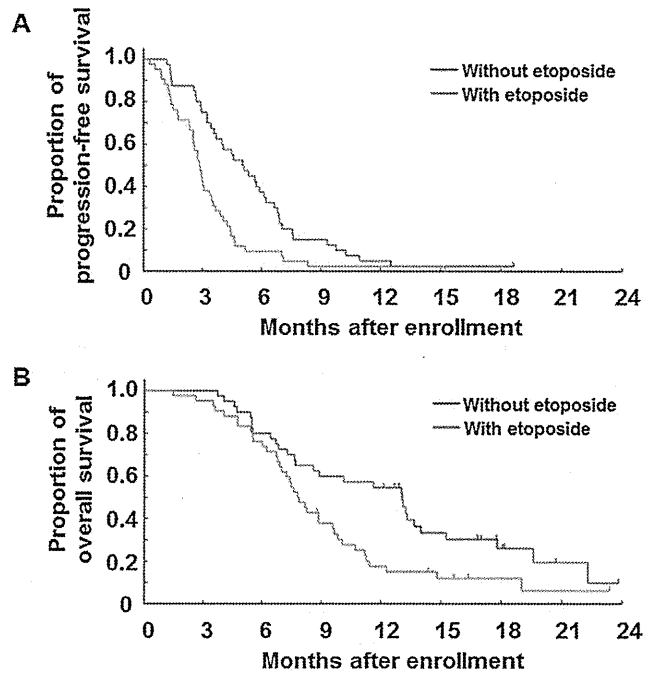

Fig. 2. (A) Progression-free survival and (B) overall survival in patients previously treated with etoposide ($n = 42$) and those not treated with etoposide ($n = 40$).

gender, performance status, disease extent at entry, number of prior chemotherapy regimens, prior treatment with irinotecan, response to prior chemotherapy (CR/PR *v* SD/PD), or history of thoracic radiation therapy].

3.3. Survival

At the cutoff date for data collection, the median follow-up time was 8.8 months in all registered patients (range, 1.5–23.8 months). Of the 82 patients, 81 (98.8%) were observed until disease progression and 66 (80.5%) until death. The median PFS for all 82 patients was 3.5 months (95% CI, 3.0–4.3 months) and the PFS at 6 months was 23.2% (95% CI, 14.7–32.7%; Fig. 1A). The median OS for all 82 patients was 8.9 months (95% CI, 7.6–11.3 months) and the 1-year survival was 35.7% (95% CI, 25.4–46.1%; Fig. 1B).

PFS was shorter in patients previously treated with etoposide than in others (median, 2.9 *v* 5.1 months; hazard ratio, 2.11; 95% CI, 1.35–3.30; $P = 0.0009$; Fig. 2A), as was OS (median, 7.9 *v* 13.1 months; hazard ratio, 1.86; 95% CI, 1.13–3.06; $P = 0.0128$; Fig. 2B).

3.4. Safety

The most common adverse events were hematological toxicities, including grade-3 or -4 neutropenia (93.9%), leukopenia (85.4%), anemia (25.6%), and thrombocytopenia (20.7%; Table 4). Grade-3 febrile neutropenia developed in 22 patients (26.8%). Nonhematological toxicities were generally mild and no evidence of cardiotoxicity of AMR was found in this study (Table 4). Pneumonitis was observed in nine patients (grade 4, $n = 1$; grade 3, $n = 2$; grade 2, $n = 3$; and grade 1, $n = 3$), and seven (grade 4, $n = 1$; grade 3, $n = 2$; grade 2, $n = 2$; and grade 1, $n = 2$) discontinued treatment because of unacceptable toxicity levels. The incidence rate of pneumonitis was higher in patients with history of thoracic radiation therapy than in others (38.5% *v* 5.8%, respectively), but one grade 4 pneumonitis case was observed in a patient without a history of thoracic radiation therapy.

Table 4
Grade 3 or 4 adverse events in patients treated with amrubicin ($N = 82$) (CTCAE v3.0).

Adverse event	Grade 3		Grade 4		≥Grade 3	
	n	%	*n*	%	*n*	%
Leukopenia	48	58.5	22	26.8	70	85.4
Anemia	19	23.2	2	2.4	21	25.6
Thrombocytopenia	12	14.6	5	6.1	17	20.7
Neutropenia	18	22.0	59	72.0	77	93.9
Febrile neutropenia	22	26.8	0	0.0	22	26.8
Hyperglycemia	11	16.4	0	0.0	11	16.4
Hyponatremia	9	11.0	4	4.9	13	15.9
Infection	5	6.1	1	1.2	6	7.3
Dyspnea	3	3.7	1	1.2	4	4.9
Elevated ALT level	4	4.9	0	0.0	4	4.9
Elevated AST level	3	3.7	0	0.0	3	3.7
Anorexia	3	3.7	0	0.0	3	3.7
Pneumonitis	2	2.4	1	1.2	3	3.7
Fatigue	1	1.2	0	0.0	1	1.2
Weight loss	1	1.2	0	0.0	1	1.2
Nausea	1	1.2	0	0.0	1	1.2
Sensory neuropathy	1	1.2	0	0.0	1	1.2

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.

G-CSF was administered to 51 (62.2%) patients and blood transfusions were necessary in 9 (11.0%). No treatment-related death was observed in this study.

4. Discussion

This single-arm confirmatory study was conducted to confirm the efficacy and safety of AMR in patients with refractory SCLC. In the present study, the primary endpoint was the ORR, which was 32.9%. This data supported the result that the ORR of AMR therapy was significantly better than that of topotecan therapy, in accordance with that previously reported in a randomized phase II study by Inoue et al. [9]. A possible limitation of this study is related to its design, which was not a randomized phase III study, but rather a nonrandomized single-arm confirmatory study. Although there was potential for selection bias as a result of this study design, ORR

was sufficiently higher than that for topotecan therapy in previous studies [8,11]. The secondary endpoints, PFS and OS, were also favorable, and no treatment-related deaths occurred in this study. On the basis of these results, we conclude that AMR monotherapy is suitable as an effective and safe treatment option for refractory SCLC.

Jotte et al. [15] reported the results of a randomized phase III trial of AMR versus topotecan as second-line treatment for SCLC. The study randomized 637 patients in a 2:1 ratio for treatment with AMR ($n = 424$) or topotecan ($n = 213$). Treatment with AMR and topotecan showed similar OS periods (median, 7.5 *v* 7.8 months; hazard ratio for death, 0.880; 95% CI, 0.733–1.057; $P = 0.17$); however, higher ORRs (31.1% *v* 16.9%; $P = 0.0001$) and PFS periods (median, 4.1 *v* 3.5 months; hazard ratio for death or disease progression, 0.802; 95% CI, 0.667–0.965; $P = 0.0182$) were found with AMR therapy, and toxicity levels were more acceptable than those with topotecan therapy. Furthermore, in a subset analysis of 295 patients with refractory SCLC, AMR therapy demonstrated a modest improvement in OS (median, 6.2 *v* 5.7 months; hazard ratio for death, 0.766; 95% CI, 0.589–0.997; $P = 0.0469$). These results support our assertion that AMR monotherapy is a reasonable treatment option for patients with refractory SCLC.

In this study, a subgroup analysis revealed that prior treatment with etoposide, a topoisomerase II inhibitor, was associated with a poorer response to AMR and poor survival. Ettinger et al. [16] reported the results of a phase II study of AMR as a second-line therapy for patients with platinum-refractory SCLC. In total, 75 American and European patients were enrolled, of whom, 67 (89.3%) were pretreated with a chemotherapy regimen including etoposide. The confirmed ORR of AMR therapy was 21.3% (95% CI, 12.7–32.3%) and the median PFS was 3.2 months (95% CI, 2.4–4.0 months). These efficacy data are similar to those of the patients previously treated with etoposide in the present Japanese study. Therefore, previous chemotherapy with etoposide, but not ethnic differences, may have influenced the efficacy of AMR therapy. Preclinical studies [17–20] have suggested that treatment with topoisomerase I inhibitors results in downregulation of the topoisomerase I target and reciprocal upregulation of topoisomerase II, thereby causing hypersensitivity to topoisomerase II inhibitors. Conversely, treatment with topoisomerase II inhibitors results in downregulation of topoisomerase II and upregulation of topoisomerase I. These results may explain why prior treatment with etoposide was associated with a lower response to AMR therapy in the present study.

Although etoposide plus cisplatin (EP) is considered the standard first-line chemotherapy for patients with extensive-stage SCLC in Western countries, irinotecan, a topoisomerase I inhibitor, plus cisplatin (IP) is generally used for Japanese patients, which is based on the results of a previous phase III study comparing IP with EP for extensive-stage SCLC (JCOG9511) [2]. AMR may also play an important role in the treatment of refractory SCLC, especially for patients previously treated with IP. In a recent Japanese phase III study comparing AMR plus cisplatin (AP) with IP for the treatment of extensive-stage SCLC (JCOG0509) [21], similar PFS periods were found for AP and IP (median, 5.1 *v* 5.7 months), but AP was inferior to IP in terms of OS (median, 15.3 *v* 18.0 months). Over 90% patients in both groups received subsequent chemotherapy. The most commonly administered drugs after the termination of treatment were topotecan in the AP group and AMR in the IP group. Subsequent chemotherapy with AMR may have contributed to the longer OS period in the IP group.

The most common severe toxicity associated with AMR therapy in the present study was myelosuppression in the form of neutropenia. No treatment-related death was observed, which was probably because of the reasonable protocol-specified dose reductions and/or treatment delays. However, patients experienced febrile neutropenia more frequently in the present study (26.8%) than in previous studies (5.0–13.8%) [9,13,16]. According to the guidelines of the American Society of Clinical Oncology, prophylactic G-CSF use is clinically effective when the risk of febrile neutropenia is 20% [22]. To decrease the incidence of febrile neutropenia in patients treated with AMR for refractory SCLC, aggressive treatment of myelosuppression, including prophylactic G-CSF use, should be considered. Nonhematological toxicity was generally mild, but the treatment was terminated in eight patients (9.8%) because of unacceptable toxicity levels, including pneumonitis in seven. Although no death was associated with pneumonitis in the present study, careful monitoring for the development of pneumonitis is necessary. Similar to previous studies [9,13,16], no evidence of anthracycline-induced cardiotoxicity was found.

In conclusion, AMR monotherapy for refractory SCLC showed a favorable tumor response, prolonged survival, and acceptable toxicity, especially in patients not previously treated with etoposide. Therefore, AMR monotherapy presents a standard treatment option for refractory SCLC.

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Previous presentation of the manuscript:

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Clinical trial registration: UMIN000002763 (http://www.umin.ac.jp/ctr/).

Conflict of interest statement

The authors report no conflicts of interest that could inappropriately influence this work.

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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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