Received: 13 April 2021 | Accepted: 18 May 2021

DOI: 10.1111/1759-7714.14048

ORIGINAL ARTICLE

WILEY

Randomized phase 2 study comparing irinotecan versus amrubicin as maintenance therapy after first-line induction therapy for extensive disease small cell lung cancer (HOT1401/NJLCG1401)

Hisashi Tanaka[1] | Yukihiro Hasegawa[2] | Yuka Fujita[3] | Atsushi Nakamura[4] | Eiki Kikuchi[5] | Yasutaka Kawai[6] | Toshiyuki Harada[7] | Naomi Watanabe[8] | Hiroshi Yokouchi[9,10] | Kazuhiro Usui[11] | Ryota Saito[12] | Hiroshi Watanabe[13] | Tomomi Masuda[14] | Tatsuro Fukuhara[15] | Keita Kudo[16] | Ryoichi Honda[17] | Satoshi Oizimi[5,10] | Makoto Maemondo[18] | Akira Inoue[19] | Naoto Morikawa[18,19]

[1]Department of Respiratory Medicine, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

[2]Department of Respiratory Medicine, Aomori Prefectural Central Hospital, Aomori, Japan

[3]Department of Respiratory Medicine, National Hospital Organization Asahikawa Medical Center, Asahikawa, Japan

[4]Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan

[5]First Department of Medicine, Hokkaido University Hospital, Sapporo, Japan

[6]Department of Respiratory Medicine, Oji General Hospital, Tomakomai, Japan

[7]Department of Respiratory Medicine, JCHO Hokkaido Hospital, Sapporo, Japan

[8]Department of Respiratory Medicine, Sunagawa City Medical Center, Sunagawa, Japan

[9]Department of Pulmonary Medicine, Fukushima Medical University School of Medicine, Fukushima, Japan

[10]Department of Respiratory Medicine, National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan

[11]Division of Respirology, NTT Medical Center Tokyo, Tokyo, Japan

[12]Department of Respiratory Medicine, Tohoku University School of Medicine, Sendai, Japan

[13]Department of Respiratory Medicine, Saka General Hospital, Shiogama, Japan

[14]Department of Respiratory Medicine, Gunma University, Maebashi, Japan

[15]Department of Respiratory Medicine, Miyagi Cancer Center, Natori, Japan

[16]Department of Medical Oncology and Respiratory Medicine, National Hospital Organization Osaka Minami Medical Center, Osaka, Japan

[17]Department of Respiratory Medicine, Asahi General Hospital, Chiba, Japan

[18]Division of Pulmonary Medicine, Allergy, and Rheumatology, Iwate Medical University Faculty of Medicine Graduate School of Medicine Morioka, Iwate, Japan

[19]Department of Palliative Medicine, Tohoku University School of Medicine, Sendai, Japan

Correspondence
Hisashi Tanaka, Department of Respiratory Medicine, Hirosaki University Graduate School of Medicine. 5 Zaifu-cho, Hirosaki 036-8562, Japan.
Email: xyghx335@gmail.com

Abstract

Background: A cisplatin plus irinotecan (CPT-11) regimen is used for patients with extensive disease small cell lung cancer (ED-SCLC). Amrubicin (AMR) is primarily used for relapsed SCLC. The HOT1401/NJLCG1401 trial, an open-label randomized phase II trial, was designed to assess the benefit of maintenance therapy in patients with ED-SCLC who responded to induction therapy.

Methods: Patients with histologically- or cytologically-confirmed ED-SCLC were included and were treated with an induction therapy of four cycles of cisplatin (60 mg/m^2 on day 1) plus CPT-11 (60 mg/m^2 on days 1, 8, and 15) every

Clinical Trial Number: UMIN 000013882.

four weeks. After induction therapy, patients who had nonprogressive disease were randomized to receive either maintenance CPT-11 (60 mg/m^2 on days 1 and 8) every three weeks, or AMR (35 mg/m^2 on days 1–3) every three weeks.

Results: A total of 34 patients were enrolled; 20 patients had progressive disease or received incomplete induction chemotherapy. Finally, 14 patients were randomly assigned to receive CPT-11 (n = 7) or AMR (n = 7). This study was terminated prematurely because of low patient accrual. The overall objective response rate was 73%, the median PFS was 5.7 months (95% confidence interval [CI]: 3.6–11.8), and the median overall survival was 20.1 months (95% CI: 13.7–not reached). No statistically significant difference in progression-free survival (PFS) were noted between patients treated with CPT-11 and those treated with AMR. There were no treatment-related deaths in this study.

Conclusions: Maintenance therapy with CPT-11 or AMR after induction therapy might be effective in some patients.

KEYWORDS
amrubicin, cisplatin, irinotecan, maintenance, small-cell lung cancer

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide.[1] Small cell lung cancer (SCLC) accounts for 10% of clinical lung cancer cases and is clinically different from non-small cell lung cancer (NSCLC) by having a rapid doubling time and high growth rate, with over 70% of patients being diagnosed with extensive disease (ED) at the time of diagnosis.[2,3] Although SCLC is typically responsive to initial chemotherapy, most patients relapse within six months after completing their initial treatment, leading to a median survival of approximately 13 months for patients with ED-SCLC; <5% of patients with ED survive two years.[4,5] In the past several decades, platinum-based chemotherapy has been used as the preferred first-line treatment for patients with ED-SCLC. Platinum plus etoposide is the most commonly used first-line chemotherapy regimen in the US and Europe based on phase III clinical trials.[6,7] The Japan Clinical Oncology Group (JCOG) 9511 trial demonstrated that cisplatin plus irinotecan (CPT-11) improved overall survival (OS) compared with a cisplatin plus etoposide regimen in patients with ED-SCLC.[8] Amrubicin (AMR) was approved for the treatment of SCLC in 2002 in Japan. AMR demonstrated a high response rate (31.1% with amrubicin and 16.9% with topotecan) and improved survival in patients with refractory relapsed SCLC.[9] Several phase II studies have also reported the efficacy of AMR for patients with relapsed SCLC.[10–12] Conversely, in the first-line setting, a previous randomized phase III trial was conducted to confirm the noninferiority of AMR plus cisplatin compared with CPT-11 plus cisplatin in terms of OS. However, the AMR-based chemotherapy was inferior to the CPT-11 plus cisplatin regimen (15.0 vs. 17.7 months; AMR arm: hazard ratio [HR], 1.43).[13] Antivascular endothelial growth factor therapy in SCLC also failed to display efficacy in improving OS. In the GOIRC-AIFA trial, 204 treatment-naive patients with ED-SCLC received cisplatin plus etoposide or the same regimen with bevacizumab every three weeks, followed by bevacizumab. The study showed a statistically significant improvement in progression-free survival (PFS; 5.7 vs. 6.7 months, $p = 0.030$) in the experimental arm; however, there was no significant improvement in OS (8.9 vs. 9.8 months, $p = 0.113$).[14] This finding was observed in unsuccessful phase III clinical trials conducted over the past several decades.

Maintenance chemotherapy with cytotoxic agents is widely used for patients with NSCLC.[15] On the other hand, the benefits of maintenance chemotherapy in patients with SCLC remain unclear. A meta-analysis of 1806 patients enrolled in a large-scale study indicated that maintenance chemotherapy with cytotoxic agents did not improve survival in patients with SCLC. However, a significant advantage was observed in terms of PFS for maintenance chemotherapy in patients with ED-SCLC (HR, 0.72; $p = 0.003$).[16] The efficacy of maintenance chemotherapy by cytotoxic agents has not yet been clarified. Therefore, we conducted an open-label randomized phase II trial to assess the benefit of maintenance therapy in patients with ED-SCLC who responded to induction therapy.

METHODS

Study design

This clinical trial was an open-label randomized phase II study conducted in two lung cancer study groups (Hokkaido Lung Cancer Clinical Study Group and North Japan Lung Cancer Study Group). This study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the institutional review boards of all participating institutions (Hirosaki University Graduate School of Medicine, Aomori Prefectural Central Hospital, National Hospital Organization Asahikawa Medical Center, Sendai Kousei Hospital, Hokkaido University Hospital, Oji General

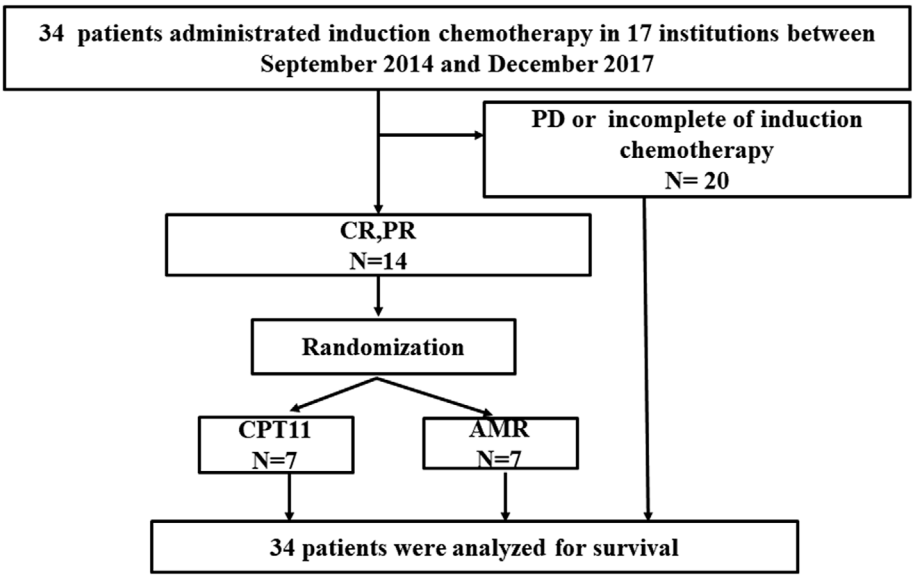

FIGURE 1 Study flow diagram showing the study population for analysis. AMR, amrubicin; CPT-11, irinotecan; CR, complete response; PD, progressive disease; PR, partial response

TABLE 1 Patient characteristics

Characteristic	Induction *N* (%)	Maintenance (CPT-11) *N* (%)	Maintenance (AMR) *N* (%)
Total number of patients	34	7	7
Gender			
Male	24 (70.5)	4 (57.1)	4 (57.1)
Female	10 (29.5)	3 (42.9)	3 (42.9)
Age (years), median (range)	66 (49–74)	69 (56–71)	68 (54–74)
71≦	6 (17.6)	2 (28.5)	1 (14.3)
ECOG PS			
0–1	30 (80.3)	7 (100)	7 (100)
2	4 (11.7)	0	0
Smoker	34 (100)	7 (100)	7 (100)
BI, median (range)	877 (400–1920)	820 (525–1320)	800 (400–1880)
ProGRP, median (range)	708 (26.9–6043)	1924 (505–5854)	1980 (32.3–4640)
ProGRP before maintenance therapy	-	54.8 (31.9–323)	55.9 (31.5–184)
Metastatic site			
Brain	6 (17.6)	1 (14.2)	1 (14.2)
Liver	7 (20.5)	2 (28.5)	2 (28.5)
Response after induction therapy			
CR	4 (11.7)	2 (28.5)	1 (14.3)
PR	13 (38.3)	5 (71.5)	6 (85.7)
SD	1 (2.9)	0	0
PD	10 (29.5)	0	0
NE	6 (17.6)	0	0

Abbreviations: AMR, amrubicin; BI, Brinkman index; CPT-11, irinotecan; CR, complete response; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PR, partial response; ProGRP, progastrin releasing peptide; PS, performance status; NE, not evaluated; SD, stable disease.

Hospital, JCHO Hokkaido Hospital, Sunagawa City Medical Center, Fukushima Medical University School of Medicine, National Hospital Organization Hokkaido Cancer Center, NTT Medical Center Tokyo, Tohoku University School of Medicine, Saka General Hospital, Gunma University, Miyagi Cancer Center, National Hospital Organization Osaka Minami Medical Center, Asahi General Hospital, and Iwate Medical University). All patients provided written informed

TABLE 2 Treatment delivery and supportive treatment

	Number of patients (%)		
	Induction ($N = 34$)	**Maintenance (CPT-11) ($N = 7$)**	**Maintenance (AMR) ($N = 7$)**
Complete	24 (70.6)	-	-
Incomplete	10 (29.4)	-	-
Treatment cycle median (range)	3 (1–4)	5 (1–23)	9 (1–26)
Dose reduction	9 (26.4)	0	0
GCSF	5 (14.7)	0	3 (23.3)
RBC transfusion	0	0	0
Platelet transfusion	0	0	0

Abbreviations: AMR, amrubicin; CPT-11, irinotecan; GCSF, granulocyte-colony stimulating factor; RBC, red blood cell.

consent before treatment. This study was registered in the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (Trial number: UMIN 000013882).

Eligibility criteria

Patients aged 20–74 years with histologically- or cytologically-confirmed ED-SCLC were included. In the JCOG 9511 study, a phase III trial include patients aged 20–70, on the other hand patients aged 71 and over were included in the global phase 3 trial. We decided to include patients aged 20–74 years in our study. The patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2 and adequate bone marrow function (neutrophil count ≥1500/mm^3, hemoglobin ≥9.0 g/dl, and platelet count ≥100 000/mm^3). They also displayed adequate function of other organs, which was assessed using aspartate transaminase and alanine transaminase levels of ≤100 IU/L, total bilirubin level of ≤1.5 mg/dl, serum creatinine level of ≤1.5 mg/dl, $PaO_2 \geq 60$ torr, or $SpO_2 \geq 95\%$; a life expectancy of >2 months was also required. Patients who were pregnant or lactating, had symptomatic brain metastases, used corticosteroids, and those who had medical problems such as active peptic ulcer, heart disease, diabetes mellitus, cerebrovascular disease, UGT1A1*6 and UGT1A1*28 mutant genotypes, interstitial pneumonia, or pulmonary fibrosis were excluded. The main eligibility criteria for maintenance therapy were as follows: ECOG PS of 0–1 and achievement of complete remission (CR), partial response (PR), or stable disease (SD) after induction therapy. Patients who received prophylactic cranial irradiation or patients who could not complete four cycles of induction cisplatin plus CPT-11 therapy were excluded.

Treatment schedule

All patients received 60 mg/m^2 of cisplatin administered intravenously on day 1 and 60 mg/m^2 of CPT-11 administered intravenously on days 1, 8, and 15 every four weeks for four cycles during induction therapy. Study treatment was terminated if progressive disease (PD) or unacceptable toxicity were observed in the patient, the patient rejected further treatment, or the physician decided to discontinue treatment. Patients who attained CR, PR, or SD after induction therapy were randomized to the CPT-11 arm or the AMR arm for treatment. In the CPT-11 arm, 60 mg/m^2 of irinotecan was administered on days 1 and 8 every three weeks until PD was noted. In the AMR arm, 35 mg/m^2 of amrubicin was administered on days 1–3 every three weeks until PD was noted. In the event of grade 4 neutropenia persisting for ≥4 days, grade 4 thrombocytopenia, febrile neutropenia, or nonhematological toxicity of grade ≥3 during the previous courses, the dose of CPT-11 was reduced by 10 mg/m^2 or the dose of AMR was reduced by 5 mg/m^2. Study treatment was discontinued if further dose reduction was required.

Evaluation and statistical analysis

The primary endpoint was six-month PFS rate. In the JCOG 9511 study, a phase III trial, the six-month PFS rate of patients treated with cisplatin plus irinotecan was 65%. Thus, we assumed that a six-month PFS rate of 75% among eligible patients indicates efficacy. This study was designed to have 80% power to accept the hypothesis and a one-sided type I error of 10% significance to reject the hypothesis. The estimated accrual number was 38 patients in each arm. Allowing for a certain number of dropouts, the accrual number was determined to be 80 patients. The secondary endpoints were PFS, OS, one-year survival rate, toxicity profiles, and the rate of maintenance therapy. We estimated OS and PFS using the Kaplan–Meier method, and the groups were compared using the log-rank test. A p-value of <0.05 was considered to indicate a statistically significant difference. PFS was calculated from the day of treatment until disease progression, or death from any cause and was censored at the date of the last follow-up in patients who terminated treatment without disease progression. If other cancer therapy was initiated before PD occurred, the patient was censored on the

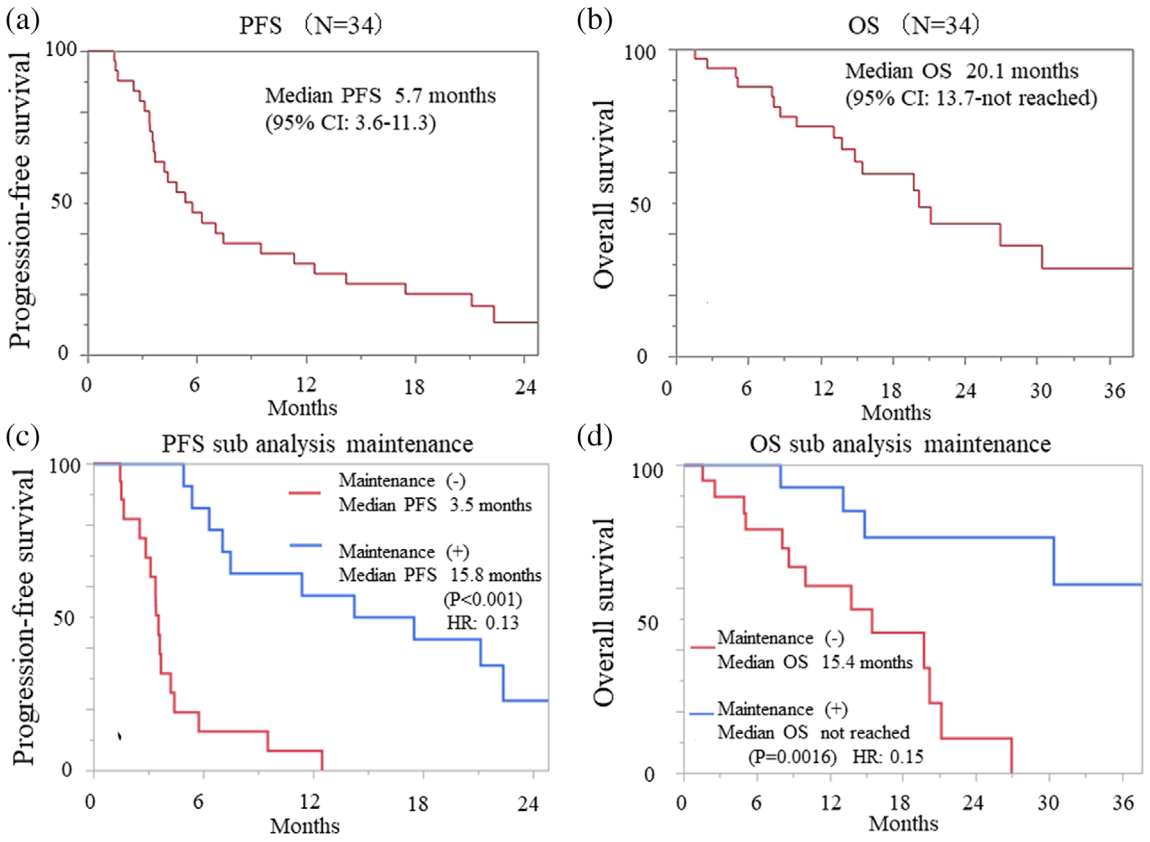

FIGURE 2 (a) Kaplan–Meier analysis of progression-free survival (PFS) for all 34 treated patients. (b) Kaplan–Meier analysis of overall survival (OS) for all 34 treated patients. (c) Kaplan–Meier analysis of PFS with and without maintenance therapy. (d) Kaplan–Meier analysis of OS with and without maintenance therapy

date when the other therapy began. OS was defined as the time from the date of enrollment to the date of death or the last follow-up. Statistical analyses were performed using JMP 13 (SAS Institute). Toxicities were assessed according to the National Cancer Institute-Common Toxicity Criteria, version 4.0. Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).

RESULTS

Patient characteristics

From September 2014 to December 2017, 34 patients were enrolled. However, this study was terminated prematurely because of low patient accrual. A total of 20 patients had PD or incomplete induction chemotherapy; thus, 14 (41.2%) patients were randomly assigned to receive either CPT-11 ($n = 7$) or AMR ($n = 7$) (Figure 1). The patient characteristics are shown in Table 1. The median age was 66 (range, 49–74) years, 70.5% of the patients were male, and most (80.3%) patients had an ECOG PS score of 0 or 1. All patients had a smoking history. There were no cases of SD in the maintenance phase.

Treatment administration, dose reduction, discontinuation, and compliance

Treatment delivery and supportive treatment are summarized in Table 2. The completion rate of induction therapy was 70.6% (24/34). Dose reduction was necessary in nine (26.4%) patients during induction therapy. Five (14.7%) patients required granulocyte colony stimulating factor (G-CSF). No patients received red blood cell or platelet transfusion. Maintenance therapy was performed in 41.2% of patients. The median number of treatment cycles was five (range, 1–23) in the CPT-11 arm and nine (range, 1–26) in the AMR arm. No transfusion or dose reduction was required in either arm. Three patients received G-CSF in the AMR arm. There were 20 patients who could not move to the maintenance therapy. In total, 20 patients could not switch their treatment to maintenance therapy. PD was the primary cause why patients did not receive maintenance treatment; 10 (50%) patients presented with PD and seven (35%) did not complete four cycles of induction therapy due to toxicity. Moreover, two (10%) patients did not meet the inclusion criteria and one (5%) refused maintenance therapy.

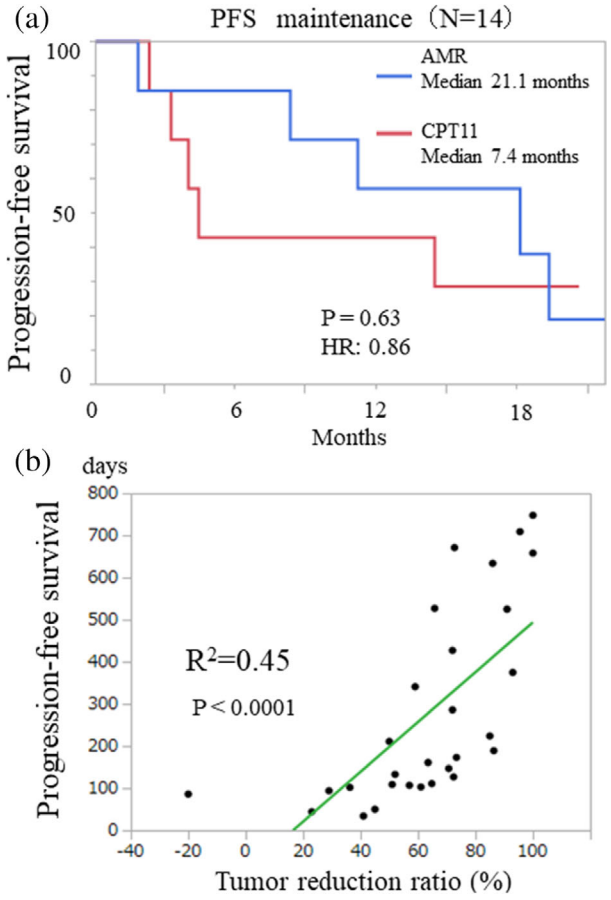

FIGURE 3 (a) Kaplan–Meier analysis of progression-free survival (PFS) with maintenance therapy by study arm. (b) Relationship between PFS and the tumor reduction ratio during induction treatments. Relationships are examined using Spearman's rank correlation coefficient

Efficacy

The overall objective response rate (ORR) was 73%. The median PFS was 5.7 months (95% CI: 3.6–11.3), and the six-month PFS rate was 47% (95% CI: 31.4–63.2) (Figure 2(a)). The median OS was 20.1 months (95% CI: 13.7–not reached) (Figure 2(b)). We conducted an additional subgroup analysis in patients with or without maintenance therapy. The subgroup analysis indicated that the patients who received maintenance therapy had a longer PFS and OS than those who did not (15.8 vs. 3.5 months, respectively, $p < 0.001$; not reached vs. 15.4 months, respectively, $p = 0.0016$) (Figure 2(c), (d)). The AMR arm had a better PFS than the CPT-11 arm, although the difference was not statistically significant (21.1 vs. 7.4 months, respectively) (Figure 3(a)). The median PFS in the maintenance phase was 8.3 months, and the median OS was not reached in either arm (Figure S1). The swimmer plot analysis showed that some patients benefited from maintenance therapy in the long term (Figure S2). There was a positive correlation between tumor shrinkage during induction therapy and PFS ($R^2 = 0.46$) (Figure 3(b)). The subgroup analysis showed that patients who achieved CR during induction therapy had a longer PFS than those who achieved PR (21.0 vs. 6.0 months, $p = 0.0009$) (Figure S3).

Toxicity analysis

The major toxicities in the induction and maintenance therapies are shown in Table 2. Hematological toxicities were the most common adverse events reported during induction chemotherapy. Grade 3 or 4 leukopenia, neutropenia, and anemia occurred in eight (23.5%), 15 (44.1%), and three (8.8%) patients, respectively. Grade 3 anorexia, nausea, and diarrhea were common nonhematological toxicities. Grade 1 or 2 nonhematological toxicities included fatigue, constipation, liver dysfunction, increased creatinine, and infection, which were generally mild and reversible. Grade 4 interstitial lung disease was observed during the first cycle of chemotherapy in one patient (2.9%), and grade 4 intracranial hemorrhage was observed during the first cycle of chemotherapy in one patient (2.9%); these were the leading causes of treatment discontinuation. There were no cases of treatment-related death. When evaluating the toxicities with maintenance CPT-11 therapy, no grade 3 hematological or nonhematological toxicities were reported. In the AMR arm, grade 3 or 4 leukopenia, neutropenia, thrombocytopenia, and febrile neutropenia occurred in three (42.8%), three (42.8%), one (14.2%), and one (14.2%) patient, respectively. In both arms, the grade 1 and 2 nonhematological toxicities were manageable (Table 3).

DISCUSSION

This is the first prospective randomized phase II study designed to evaluate the efficacy and safety of maintenance therapy in patients with ED-SCLC who responded to induction therapy in Japan. The primary endpoint was the six-month PFS rate. In the present study, the six-month PFS rate was 47% (95% CI: 31.4–63.2), which was lower than that in the previous JCOG 9511 clinical trial.[8] The present study was terminated prematurely because of low patient accrual; therefore, we were unable to make statistical conclusions. The possible reason for the low patient accrual was clinicians selected cisplatin plus etoposide regimens or carboplatin plus etoposide for patients with ED-SCLC in clinical practice. The present study demonstrated that (i) the transition rate to maintenance therapy was low, (ii) high tumor shrinkage during induction therapy is associated with a long PFS in maintenance therapy, and (iii) maintenance therapy after induction therapy was well tolerated in both the CPT-11 and AMR arms. Several possible reasons may explain the low transition rate to maintenance therapy. In the present study, the most common reason why maintenance treatment could not be performed was PD or toxicity events during induction chemotherapy. In patients with SCLC, brain metastases often appear even if the intrathoracic lesion is reduced. In our study, magnetic

TABLE 3 Toxicities during induction and maintenance therapy

Toxicities	Induction ($N = 34$)		Maintenance (CPT11) ($N = 7$)		Maintenance (AMR) ($N = 7$)	
Grade (CTCAE) v4.0	All grades *N* (%)	≥ grade3 *N* (%)	All grades *N* (%)	≥ grade3 *N* (%)	All grades *N* (%)	≥ grade3 *N* (%)
Leukopenia	24 (70.6)	8 (23.5)	2 (28.5)	0	4 (57.1)	3 (42.8)
Neutropenia	24 (70.6)	15 (44.1)	2 (28.5)	0	4 (57.1)	3 (42.8)
Anemia	24 (70.6)	3 (8.8)	4 (57.2)	0	4 (57.1)	0
Thrombocytopenia	11 (32.4)	0	0	0	2 (28.5)	1 (14.2)
Febrile neutropenia	-	3 (8.8)	-	0	-	1 (14.2)
Anorexia	24 (70.6)	5 (14.7)	2 (28.5)	0	0	0
Fatigue	13 (38.3)	1 (2.9)	2 (28.5)	0	3 (42.8)	0
Nausea	21 (61.8)	5 (14.7)	2 (28.5)	0	1 (14.2)	0
Constipation	10 (29.5)	0	0	0	1 (14.2)	0
Diarrhea	13 (38.3)	4 (11.7)	0	0	1 (14.2)	0
Alopecia	9 (26.5)	-	2 (28.5)	-	1 (14.2)	-
Creatinine increased	3 (8.8)	0	0	0	0	0
Liver dysfunction	13 (38.3)	1 (2.9)	1 (14.2)	0	2 (28.5)	0
Infection	7 (20.5)	2 (5.8)	1 (14.2)	0	1 (14.2)	0
Intracranial hemorrhage	0	1 (2.9)	0	0	0	0
Pneumonitis	1 (2.9)	1 (2.9)	0	0	0	0

Abbreviations: AMR, amrubicin; CPT11, irinotecan; CTCAE, Common Terminology Criteria for Adverse Events.

resonance imaging (MRI) assessment was necessary before proceeding to maintenance therapy. A CT scan evaluation was not acceptable, which might have affected the detection of PD in brain metastases. In this study, patients who could not complete four cycles of induction therapy were not allowed to receive maintenance therapy. If the protocol allowed the transition to maintenance therapy in three or more courses, the transition rate of maintenance therapy might be improved.

Only two prospective phase II studies have previously indicated the safety and efficacy of maintenance therapy using new generation agents after induction therapy. Han and colleagues evaluated CPT-11 (100 mg/m^2 on days 1, 8, and 15) every four weeks maintenance therapy for patients with ED-SCLC who achieved CR or PR after induction chemotherapy. The median PFS and OS in the maintenance ($n = 21$) and observation arms ($n = 24$) were 12.0 vs. 9.9 months and 17.6 vs. 20.5 months, respectively.[17] CPT-11 maintenance therapy did not further statistically improve the survival outcome. Grade 3 or 4 anemia and neutropenia were observed in 28.6% of patients. In another study, Kobayashi and colleagues evaluated the efficacy of sequential triplet chemotherapy consisting of three cycles of cisplatin and CPT-11 followed by three cycles of AMR in patients with ED-SCLC.[18] The ORR was 79%, median PFS was 6.5 months, and median OS was 15.4 months. This study cannot be defined as strict maintenance chemotherapy; however, it is the first report to evaluate the efficacy of AMR after induction chemotherapy. The median PFS in our study was lower than the values in these two studies. The difference was due to the number of patients who transitioned to maintenance therapy. In the present study, the rate of patients receiving maintenance therapy was low (41.2%). However, the OS was 20.1 months, which was comparatively longer than that reported in the previous two studies. There are a few possible reasons why the OS in the present study was longer than that in previous studies. First, most patients received second- or third-line therapies. Second, the survival period in the maintenance transfer group was extremely good, which led to the long OS. In the present study, the median PFS of the AMR arm had a preferable tendency compared with that of the CPT-11 arm. Patients who achieved high tumor shrinkage during induction chemotherapy tended to have a longer maintenance term. Generally, maintenance therapy must be less toxic and well tolerated, and our results indicated that both maintenance arms were well tolerated. In terms of toxicity, the CPT-11 arm appeared more tolerant than the AMR arm. In the present study, the dose schedule of CPT-11 was 60 mg/m^2, which led to fewer adverse events than those reported in a previous study.[17]

Recently, two phase III studies indicated that immune checkpoint inhibitors (ICIs) plus platinum-based chemotherapy improved PFS and OS.[19,20] The Impower 133 trial showed improvement in PFS (5.2 months in the atezolizumab arm vs. 4.3 months with placebo) and OS (12.3 vs. 10.3 months) respectively.[19] The CASPIAN trial also showed improvement in PFS (5.4 months in the

durvalumab arm vs. 5.1 months with placebo) and OS (13.0 vs. 10.3 months), respectively.[20] However, the PFS and OS in these two trials were not longer than those reported in previous studies and the present study.[8,17,18] Gadgeel et al. reported a single-arm phase II trial exploring maintenance pembrolizumab that included 45 patients with ES-SCLC who experienced PR or SD after first-line platinum-etoposide-based chemotherapy. The observed PFS was only 1.4 months.[21] Maintenance therapy with nivolumab plus ipilimumab did not prolong OS for patients with ED-SCLC.[22] Immunotherapy in SCLC requires further improvement in efficacy. Recently, updated analysis of two phase III trials KEYNOTE-189 and KEYNOTE-407 in NSCLC have been reported. The two-year OS rate was 45.5% in the pembrolizumab-combination arm versus 29.9% in the placebo arm (HR:0.56).[23] In KEYNOTE-407, the two-year OS rate was 37.5% versus 30.6% (HR: 0.71).[24] Although these studies had different histological types, the KEYNOTE-189 study indicted a preference for the addition of cytotoxic anticancer drugs and immunotherapy in maintenance therapy. It is unclear whether the maintenance combination of both cytotoxic anticancer drugs and immunotherapy could have an additional long-term tail effect. In the present study, maintenance therapy with cytotoxic drugs was well tolerated, and therefore maintenance therapy with cytotoxic drugs and immunotherapy might improve survival outcomes. Further studies may be necessary to determine whether maintenance therapy is better with cytotoxic agents. The present study has some important limitations. First, the present study was terminated prematurely. The number of patients who received maintenance therapy was too small to conclude which regimen resulted in better outcomes. Second, we did not analyze any biomarkers to predict efficacy.

This study was discontinued prematurely. Hence, it had no statistical power to reach any conclusions about the primary endpoint. However, our results showed that maintenance therapy after induction therapy might be effective in some patients. Thus, tolerance to maintenance therapy should be considered in future studies with a large cohort.

ACKNOWLEDGMENTS

We thank the patients and their families and all the investigators.

CONFLICT OF INTEREST

Atsushi Nakamura received honoraria from MSD, AstraZeneca, Chugai Pharma, Kyowa Hakko Kirin, Nippon Boehringer Ingelheim, Taiho Pharmaceutical. The rest of the authors declare that they have no competing interests.

ORCID

Hisashi Tanaka https://orcid.org/0000-0003-2009-0210

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67:7–30.
2. Gustafsson BI, Kidd M, Chan A, Malfertheiner MV, Modlin IM. Bronchopulmonary neuroendocrine tumors. Cancer. 2008;113:5–21.
3. Travis WD, Travis LB, Devesa SS. Lung cancer. Cancer. 1995;75(Suppl 1):191–202.
4. Rudin CM, Ismaila N, Hann CL, Malhotra N, Movsas B, Norris K, et al. Treatment of small-cell lung cancer: American Society of Clinical Oncology endorsement of the American College of Chest Physicians guideline. J Clin Oncol. 2015;33:4106–11.
5. Chute JP, Chen T, Feigal E, Simon R, Johnson BE. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. J Clin Oncol. 1999;17:1794–801.
6. Hanna N, Bunn PA Jr, Langer C, Einhorn L, Guthrie T, Beck T, et al. Randomized phase III comparing irinotecan/cisplatin with etoposide/cisplatin in patient with previously untreated extensive-staged disease small-cell lung cancer. J Clin Oncol. 2006;24:2038–43.
7. Lara PN Jr, Gandara DR, Natale RB. Randomized phase III trial of irinotecan/cisplatin versus etoposide/cisplatin in patients with extensive-stage small-cell lung cancer. Clin Lung Cancer. 2006;7:353–6.
8. Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive disease small-cell lung cancer. N Engl J Med. 2002;346:85–91.
9. von Pawel J, Jotte R, Spigel DR, O'Brien ME, Socinski MA, Mezger J, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. J Clin Oncol. 2014;32:4012–9.
10. Inoue A, Sugawara S, Yamazaki K, Maemondo M, Suzuki T, Gomi K, et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. J Clin Oncol. 2008;26:5401–6.
11. Murakami H, Yamamoto N, Shibata T, Takeda K, Ichinose Y, Ohe Y, et al. A single-arm confirmatory study of amrubicin therapy in patients with refractory small-cell lung cancer: Japan Clinical Oncology Group Study (JCOG0901). Lung Cancer. 2014;84:67–72.
12. Ettinger DS, Jotte R, Lorigan P, Gupta V, Garbo L, Alemany C, et al. Phase II study of amrubicin as second-line therapy in patients with platinum-refractory small-cell lung cancer. J Clin Oncol. 2010;28:2598–603.
13. Satouchi M, Kotani Y, Shibata T, Ando M, Nakagawa K, Yamamoto N, et al. Phase III study comparing amrubicin plus cisplatin with irinotecan plus cisplatin in the treatment of extensive-disease small-cell lung cancer: JCOG0509. J Clin Oncol. 2014;32:1262–8.
14. Tiseo M, Boni L, Ambrosio F, Camerini A, Baldini E, Cinieri S, et al. Italian, multicenter, phase III, randomized study of cisplatin plus etoposide with or without bevacizumab as first-line treatment in extensive-disease small cell lung cancer: the GOIRC-AIFA FARMPMFJM trial. J Clin Oncol. 2017;35:1281–7.
15. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (paramount): a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2012;13:247–55.
16. Zhou H, Zeng C, Wei Y, Zhou J, Yao W. Duration of chemotherapy for small cell lung cancer: a meta-analysis. PLoS One. 2013;8:e73805.
17. Han JY, Kim HT, Lim KY, Yoon SJ, Lee DH, Lee JS. Randomized phase II study of maintenance irinotecan therapy versus observation following induction chemotherapy with irinotecan and cisplatin in extensive disease small cell lung cancer. J Thorac Oncol. 2008;3:1039–45.
18. Kobayashi M, Matsui K, Iwamoto Y, Ebi N, Oizumi S, Takeda K, et al. Phase II study of sequential triplet chemotherapy, irinotecan and cisplatin followed by amrubicin, in patients with extensive-stage small cell lung cancer: West Japan Thoracic Oncology Group Study 0301. J Thorac Oncol. 2010;5:1075–80.

19. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379:2220–9.
20. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (Caspian): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394:1929–39.
21. Gadgeel SM, Pennell NA, Fidler MJ, Halmos B, Bonomi P, Stevenson J, et al. Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). J Thorac Oncol. 2018;13:1393–9.
22. Owonikoko TK, Park K, Govindan R, Ready N, Reck M, Peters S, et al. Nivolumab and ipilimumab as maintenance therapy in extensive-disease small-cell lung cancer: CheckMate 451. J Clin Oncol. 2021;39:1349–59.
23. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. J Clin Oncol. 2020;38:1505–17.
24. Paz-Ares L, Vicente D, Tafreshi A, Robinson A, Soto Parra H, Mazières J, et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol-specified final analysis of KEYNOTE-407. J Thorac Oncol. 2020;15:1657–69.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Tanaka H, Hasegawa Y, Fujita Y, et al. Randomized phase 2 study comparing irinotecan versus amrubicin as maintenance therapy after first-line induction therapy for extensive disease small cell lung cancer (HOT1401/NJLCG1401). Thorac Cancer. 2021;12:2113–2121. https://doi.org/10.1111/1759-7714.14048