


ORIGINAL ARTICLE

A pilot study of adjuvant chemotherapy with carboplatin and oral S-1 for patients with completely resected stage II to IIIA non-small cell lung cancer

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Keywords

Adjuvant chemotherapy; carboplatin; lung cancer; pulmonary embolism; S-1.

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Abstract

Background: Adjuvant chemotherapy with platinum-based regimens for completely resected early-stage non-small cell lung cancer (NSCLC) provides overall survival benefit in several clinical trials.

Objectives: We conducted this prospective study to evaluate the efficacy and safety of adjuvant chemotherapy with carboplatin and S-1 for patients with completely resected stage II to IIIA NSCLC.

Methods: Patients with completely resected stage IIA to IIIA NSCLC were treated with four cycles of carboplatin with area under the concentration time curve of 5 mg/mL/min on day 1 plus S-1 at 80–120 mg/bodyweight per day for two weeks, followed by one-week rest as adjuvant chemotherapy. The primary endpoint was the completion rate of three cycles of the treatment. The secondary endpoints were safety and two-year survival rate.

Results: A total of 19 patients were enrolled, until the study was terminated prematurely because of fatal pulmonary embolism in two patients. The median number of treatment cycles was three (range: 1–4). The completion rate of three cycles was 78.9% (95% confidence interval [CI]: 56.6–91.4%). Two-year disease-free survival rate was 57.8%. Grade 3 or 4 hematological toxicities included neutropenia (26.2%), anemia (5.2%), and thrombocytopenia (15.7%). Grade 3 or 4 nonhematological toxicities were anorexia (10.5%) and nausea (10.5%). Febrile neutropenia developed in 5.2%. In two patients (10.5%), grade five pulmonary embolism was observed, and the causal relationship with treatment could not be denied.

Conclusions: Carboplatin and oral S-1 had modest survival benefit, but this regimen was not tolerable in an adjuvant setting because fatal pulmonary embolism occurred in two patients.

Key points

- Carboplatin and oral S-1 had modest survival benefit but this regimen was not tolerable.
- Fatal pulmonary embolism occurred in this regimen.

Introduction

Lung cancer is the leading cause of death related to cancer worldwide.¹ Surgery is considered to be the primary treatment modality for early stage non-small cell lung cancer (NSCLC), although only 20%–25% of tumors are suitable for potentially curative resection in patients with pathological stage IIA to IIIA NSCLC.² The rationale for adjuvant chemotherapy for patients with early-stage lung cancer is based on the observations that distant metastases are the most common site of recurrence after potentially curative surgery. The efficacy of postoperative adjuvant chemotherapy including cisplatin for NSCLC has been previously reported.^{3–5} A large-scale study of cisplatin-based postoperative chemotherapy (the Lung Adjuvant Cisplatin Evaluation [LACE]) indicated that the hazard ratio against death in all patients was 0.89 (95% confidence interval [CI]: 0.82–0.96), and five-year survival benefit was 5.4%.⁶ In addition, five-year overall survival (OS) rate was approximately 70% in patients with stage II to IIIA NSCLC who underwent postoperative adjuvant chemotherapy.⁷ Although cisplatin plus vinorelbine and other cisplatin-based regimens are standard, severe toxicities including chemotherapy-related death are occasionally observed, which have been the problems in the adjuvant setting.⁸ In 90% of patients receiving cisplatin and vinorelbine, grade ≥ 3 toxicities were observed.⁹ Moreover, completion rate of cisplatin-based adjuvant chemotherapy was as low as 50%–70% due to toxicities such as nausea, vomiting, and nephrotoxicity.^{3,4,6} Better treatment compliance with more tolerable adjuvant chemotherapy may improve the outcomes of NSCLC patients who undergo surgery.

Carboplatin-based chemotherapy is less toxic and has relatively high completion rates. S-1 is an oral fluoropyrimidine anticancer agent that was developed in Japan. This agent combines tegafur, a prodrug of 5-fluorouracil (5-FU), with gimeracil, a reversible antagonist of the rate-limiting enzyme in the 5-FU degradation pathway, and oteracil potassium, a reversible inhibitor of the phosphoenzyme of 5-FU that reduces gastric toxicity.¹⁰ Antitumor efficacy is enhanced because of the high concentration of 5-FU in the blood.¹¹ A randomized phase III study showed the noninferiority in OS of S-1 in combination with carboplatin compared with paclitaxel in combination with carboplatin in chemo-naïve advanced NSCLC (hazard ratio, 0.928; 95% CI: 0.67–1.28).¹² In this pilot study, we aimed to evaluate the efficacy and safety of adjuvant chemotherapy with carboplatin and oral S-1 in patients with completely resected stage II to IIIA NSCLC.

Methods

Study design

This clinical trial was a prospective open-label, single-arm study conducted at our Hirosaki University Hospital

(Hirosaki, Japan). This study was performed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the institutional review board of Hirosaki University and registered at the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN000011694). A written informed consent was obtained from the study participants.

Eligibility criteria

Patients eligible for inclusion in the trial were aged 20–74 years, had histologically confirmed NSCLC that was completely resected and were pathological stage II–IIIA. The patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–1 and adequate bone marrow function (leukocyte count $\geq 4000/\text{mm}^3$, neutrophil count $\geq 1500/\text{mm}^3$, hemoglobin ≥ 9.0 g/dL, and platelet count $\geq 100\,000/\text{mm}^3$). An adequate function of other organs, including aspartate transaminase and alanine transaminase levels ≤ 100 IU/L, total bilirubin concentration ≤ 1.5 mg/dL, and creatinine ≤ 1.25 mg/dL, and $\text{PaO}_2 \geq 60$ torr, and a life expectancy more than three months were required. Patients who were pregnant or lactating, using corticosteroids or had current medical problems such as active peptic ulcer, heart disease, diabetes mellitus, cerebrovascular disease, interstitial pneumonia or pulmonary fibrosis, were excluded from the trial.

Treatment plan

Patients received carboplatin (area under the concentration time curve [AUC] 5 mg/mL/min) on day 1 and oral S-1 twice per day on days 1 to 14. The dose of S-1 was determined based on body surface area; the dose was 80 mg daily when the body surface area was <1.25 m², 100 mg daily for 1.25–1.50 m², and 120 mg daily for >1.50 m². Chemotherapy was started within four to six weeks after surgery and repeated every three weeks for four cycles. The study treatment was terminated in cases of disease progression, unacceptable toxicity or rejection of further treatment, or when the physician decided to discontinue treatment. Subsequent cycles of treatment were continued as long as the following criteria were satisfied: the leukocyte count was $\geq 1500/\text{mm}^3$, platelet count was $\geq 100\,000/\text{mm}^3$, grade of serum creatinine was ≤ 1 mg/dL, there was no infection, the ECOG PS was ≤ 1 , and the grade of any nonhematologic toxicity was ≤ 2 . In the event of grade 4 neutropenia persisting for ≥ 5 days, thrombocytopenia of grade 4, febrile neutropenia, or non-hematologic toxicity of grade ≥ 3 during the previous courses were observed, the dose of S-1 was reduced from 120 to 100 mg, from 100 to 80 mg, or from 80 to 50 mg. If these toxicities occurred after the reduction of the dose, carboplatin was reduced from AUC 5 to 4.

Evaluation and statistical analysis

The primary endpoint was the treatment completion rate. Definition of completion was administration of three cycles of carboplatin and S-1. Southwest Oncology Group (SWOG) one arm biomial was chosen to determine the number of patients required for our study. The treatment completion rate of 80% was set for the target level, with 55% as the lowest completion rate of interest. The study was designed to have 80% power to accept and a one-sided level of type I error of 5% significance to reject the hypothesis. The estimated accrual number was 21 patients. Taking ineligible patients into account, the sample size was set at 25 patients in the study. Secondary endpoints were the safety and two-year survival rate. The disease-free survival (DFS) time and OS were estimated using the Kaplan-Meier method. The DFS was defined as the time from the date of enrollment to the date of documented disease progression or death from any cause and was censored at the date of the last follow-up who terminated treatment without disease progression. The OS time was defined as the time from the date of enrollment to the date of death or last follow-up. Statistical analyses were performed using JMP 13 (SAS Institute, Cary, NC, USA). Toxicities were assessed according to the National Cancer Institute-Common Toxicity Criteria, version 4.0.

Results

Patient characteristics

Between September 2012 and August 2014, 19 patients were enrolled. This study was prematurely terminated because severe adverse events (AEs) occurred. Our safety evaluation committee decided to stop this study halfway. Patient characteristics are shown in Table 1. The median age was 64 years (range: 47–74 years), 73.7% of patients were male, and most patients (78.9%) had an ECOG PS score of 0. A total of 15 patients (78.9%) had a smoking history. Histological analysis revealed that 15 patients (78.9%) had adenocarcinoma and four (21.1%) had squamous cell carcinoma. Nine patients (47.4%) had stage IIIA disease. Seven patients (36.8%) were positive for the epidermal growth factor receptor (*EGFR*) mutation. All patients underwent lobectomy.

Treatment administration, dose reduction, discontinuation and compliance

The median number of treatment cycles was three (range: 1–4). The completion rate was 78.9% (95% CI: 56.6–91.4%). The rate of discontinuation of therapy prior to the third cycle was 21.1% (Table 2). One patient (5.2%) required dose

Table 1 Patient characteristics (*N* = 19)

	Number of patients	%
Median age (range)	64 (47–74)	
Sex		
Male	14	73.7
Female	5	26.3
ECOG PS		
0	15	78.9
1	4	21.1
Pathological stage		
IIA	2	10.5
IIB	8	42.1
IIIA	9	47.4
Surgical procedure (lobectomy)	19	100
Histological type		
Adenocarcinoma	15	78.9
Squamous cell carcinoma	4	21.1
Smoking history		
Smoker	15	78.9
Non-smoker	4	21.1
<i>EGFR</i> mutation		
Positive	7	36.8
Negative	12	63.2

ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; PS, performance status.

reduction due to grade 4 neutropenia, grade 3 febrile neutropenia, grade 3 thrombocytopenia, and grade 3 anemia.

Efficacy

The rate of local and distant recurrence was 7.0 and 37.2%, respectively. The most frequent distant recurrence was pulmonary metastasis (20.9%). Median DFS was 26.8 months (95% CI: 7.8 - not reached) (Fig 1). Two-year DFS rate was 57.8%. Median follow-up time was 45.2 months. Median OS was not reached (95% CI: 31.3- not reached) (Fig 2), and five-year OS rate was 66.7%. Clinical data of post-study treatment were available in 10 patients. Five patients were treated with *EGFR*-tyrosin kinase inhibitors, three with platinum-based chemotherapy, one with single cytotoxic agent, and one with radiotherapy.

Toxicity analysis

Table 3 shows the incidence of AEs evaluated in 19 eligible patients. Grade 3 and higher hematologic toxicities included leukopenia (5.2%), neutropenia (26.2%), anemia (5.2%), and thrombocytopenia (15.7%). Febrile neutropenia was observed in one patient (5.2%). The most common nonhematologic toxicities of grade 3 or 4 were nausea (10.5%), anorexia (10.5%). Grade 2 infection occurred in four patients (21.1%). Grade 5 pulmonary embolism (PE), which might be treatment-related, was observed in two

Table 2 Treatment administration

Median treatment cycle	Three (range, 1–4)	
Number of cycles	N	(%)
1	2	10.5
2	2	10.5
3	1	5.2
4	14	73.8
The completion rate	78.9% (95% CI: 56.6–91.4%)	
Dose reduction	1	(5.2)
Hematologic AE and FN (1)		
Discontinuation of therapy prior to the third cycle	4	(21.1)
Low compliance (1)		
Treatment delay due to neutropenia (1)		
Grade 5 pulmonary embolism (2)		

AE, adverse event; CI, confidence interval; FN, febrile neutropenia.

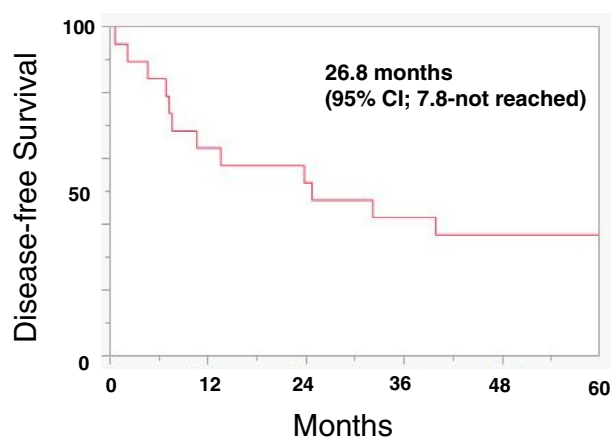


Figure 1 Kaplan-Meier analysis of the median disease-free survival for all 19 treated patients. Median disease-free survival was 26.8 months (95% CI: 7.8 - not reached). Two-year disease-free survival rate was 57.8%.

patients. In one patient, it occurred between cycle 2 and 3 who was dead on arrival at the emergency room of our hospital, and autopsy imaging indicated PE as a cause of death. The other patient developed PE between cycle 1 and 2. Both patients had no other risk factor of thrombosis than lung cancer.

Discussion

This was a prospective study designed to evaluate the safety and the efficacy of S-1 plus carboplatin for patients with completely resected early-stage NSCLC. The primary endpoint was the completion rate of three cycles of treatment. Although this study was not completed due to fatal PE in

two patients, the completion rate was 78.9%, which was higher than that reported in previous phase III clinical trials. Table 4 summarized previous large-scale phase III trials of cisplatin-based adjuvant chemotherapy and trials of S-1 based adjuvant chemotherapy. In JBR.10 and ANITA trials, 58% of the patients received three or more cycles of cisplatin, and 50% completed four cycles as planned.^{3,4}

There are reports which evaluated carboplatin-based adjuvant chemotherapy for patients with completely resected early-stage NSCLC. In a phase III CALGB9633 study, a survival benefit of postoperative carboplatin plus paclitaxel was demonstrated in stage IB NSCLC patients with tumor size of 4 cm or more.¹⁸ A total of 86% of patients completed all four cycles of chemotherapy without treatment-related deaths.¹⁸ Two prospective phase II studies which used carboplatin and S-1 for patients with completely resected NSCLC have been reported. Komazaki and colleagues reported the feasibility and compliance of adjuvant chemotherapy of S-1 (80 mg/m²) plus carboplatin (AUC 6) for patients with completely resected stage IB–IIIA NSCLC.¹³ The completion rate of three cycles was 82.4%, and they concluded adjuvant chemotherapy with S-1 plus carboplatin was well tolerated.¹³ In another study, Okumura and colleagues reported a multicenter prospective study that evaluated the feasibility of adjuvant chemotherapy with four cycles of S-1 (80 mg/m²/day for two weeks) plus carboplatin (AUC 5) followed by single-agent S-1 maintenance.¹⁴ The completion rates of four cycles of S-1 plus carboplatin and the following S-1 maintenance therapy were 89.7% and 63.2%, respectively. Two-year OS rate was 85.1%.¹⁴ In the present study, completion rate was 78.9%, which was comparable to that of the two previous trials.^{13,14}

In this study, the rate of grade 3 or 4 hematological AEs were low, and grade 3 thrombocytopenia were seen about 15%, which was comparable to the numbers in previous studies.^{13,14} Although carboplatin-based regimens are generally less emetogenic than cisplatin-based ones, higher dose of carboplatin (AUC ≥ 4) was classified as highly emetogenic chemotherapy.¹⁹ We observed that the incidence of grade three non-hematological AEs was low. The five-year OS rate was similar to the numbers shown in JBR.10 and ANITA trials. Taken together, carboplatin plus S-1 was considered less toxic but equally effective compared with cisplatin-based regimens in adjuvant chemotherapy for NSCLC.

In our study, fatal PE occurred in two patients. The risk of venous thromboembolism (VTE) is increased in patients with cancer,²⁰ and VTE is associated with worse survival outcome in cancer patients. Moreover, VTE can result in PE and other life-threatening vascular events.²¹ Kuderer and colleagues investigated treatment-related factors on the occurrence of VTE and early mortality in 1980 patients with lung cancer. A total of 122 patients developed VTE (6.1%), 47% of whom had PE.²² In our study, PE was seen

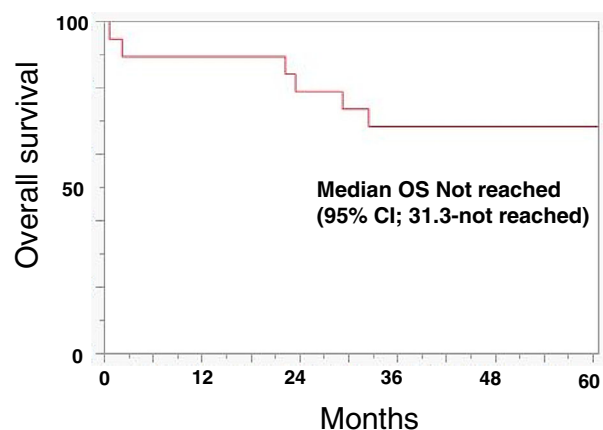


Figure 2 Kaplan-Meier analysis of overall survival for all 19 treated patients. The overall survival was not reached (95% CI: 31.3 - not reached). The five-year OS rate was 66.7%.

early after the introduction of chemotherapy. No PE event has been described in previous studies on S-1 based chemotherapy for NSCLC.¹³⁻¹⁷ Therefore, the causal relationship between chemotherapy and PE remains unclear. Both patients in our study who developed PE were female, which has been reported to be an independent predictor for VTE.²² In another report, five risk factors for VTE have been described, including primary site of cancer, prechemotherapy platelet and leukocyte counts, prechemotherapy hemoglobin or use of red cell growth factors, and body mass index,²³ although our two patients with fatal PE were not high risk. A major limitation of this study was the premature termination due to fatal PE, which made it difficult to conclude whether the primary endpoint was met or not.

In conclusion, carboplatin plus oral S-1 had modest survival benefit with high completion rate, although this regimen was not tolerable in the adjuvant setting due to fatal PE observed in two patients.

Table 3 Toxicity in patients treated with carboplatin and S-1 (N = 19)

Toxicity	Grade 1/2	%	Grade 3/4	%	Grade 5	%	≥Grade3	%
Leukopenia	10	52.6	1	5.2	0	0	1	5.2
Neutropenia	11	57.8	5	26.2	0	0	5	26.2
Anemia	10	52.6	1	5.2	0	0	1	5.2
Thrombocytopenia	10	52.6	3	15.7	0	0	3	15.7
Febrile neutropenia							1	5.2
Nausea	14	73.7	2	10.5	0	0	2	10.5
Anorexia	13	68.3	2	10.5	0	0	2	10.5
Fatigue	13	68.3	0	0	0	0	0	0
Liver dysfunction	9	47.2	0	0	0	0	0	0
Increased creatinine	6	31.5	0	0	0	0	0	0
Diarrhea	4	21.1	0	0	0	0	0	0
Constipation	18	94.8	1	5.2	0	0	1	5.2
Hyperkalemia	1	5.2	0	0	0	0	0	0
Hypokalemia	1	5.2	0	0	0	0	0	0
Infection	4	21.1	0	0	0	0	0	0
Pulmonary embolism	0	0	0	0	2	10.5	0	0

Table 4 Previous large scale phase III trial or S-1 based adjuvant chemotherapy

Reference	N	Regimen	Stage	Survival benefit	HR	Completion rates
JBR.10 [3]	482	CDDP + VNR	IB-II	69% vs. 54% (5 year)	0.7	48%
ANITA ⁴	840	CDDP+VNR	IB-IIIa	65.7 vs. 43.7 months	0.8	50%
LACE ⁶	4584	CDDP+VNR subset	I-III	Additional benefit: 5.4% (5 year)	0.8	N/A
Komazaki <i>et al.</i> ¹³	17	CBDCa+S-1	IB-IIIa	N/A	N/A	82.4% (3 cycles)
Okumura <i>et al.</i> ¹⁴	89	CBDCa+S-1 → S-1	IIa-IIIa	2-year OS 85.1%	N/A	89.7% (4 cycles) 63.2% (maintenance)
Yano <i>et al.</i> ¹⁵	30	S-1	IIa-IIIa	N/A	N/A	56.7% (8 cycles)
Tsuchiya <i>et al.</i> ¹⁶	50	S-1	IB-IIIa	3-year OS 69.4%	N/A	72% (8 cycles)
Tsuboi <i>et al.</i> ¹⁷	24	S-1	IIa-IIIa	Median OS 92.4 months	N/A	33% (9 cycles)
Present study	19	CBDCa+S-1	IIa-IIIa	DFS 59.1% 5-year OS 66.7%	N/A	78.9 (3 cycles) 73.8% (4 cycles)

CDDP; cisplatin; DFS: disease-free survival; HR, hazard ratio; N/A, not available; OS; overall survival; VNR; Vinorelbine.

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Disclosure

All authors declare they have no competing interests.

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