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A multi-institutional phase II trial of consolidation S-1 after concurrent chemoradiotherapy with cisplatin and vinorelbine for locally advanced non-small cell lung cancer

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ABSTRACT

Aim: To evaluate the efficacy and feasibility of the consolidation therapy of the oral fluoropyrimidine agent S-1 after concurrent chemoradiotherapy for unresectable stage III non-small cell lung cancer (NSCLC).

Methods: Eligible patients had unresectable stage III NSCLC with performance status of 0 or 1. Chemoradiotherapy at a total dose of 60 Gy consisted of cisplatin (80 mg/m^2) on days 1 and 29, vinorelbine (20 mg/m^2) on days 1, 8, 29 and 36. Sequential consolidation S-1 therapy was commenced at a dose of 80–120 mg twice daily on day 57 with two cycles of 4 weeks administration and 2 weeks withdrawal.

Results: Of the 66 patients, 65 were evaluated. Chemoradiotherapy was completed in 57 (87.7%) patients, and S-1 consolidation therapy was administered in 45 (69.2%) and completed in 31 (47.6%). Grade 3 pneumonitis developed in three patients with one dying of it. The response rate was 61.5% (95% confidence interval [CI], 48.6–73.3%). The median progression-free survival was 10.2 (95% CI, 8.6–13.7) months and median survival time 21.8 (95% CI, 15.6–27.6) months. The 1- and 3-year survival rates were 73.9% and 34.0%, respectively.

Conclusions: Chemoradiotherapy with cisplatin and vinorelbine followed by S-1 consolidation demonstrated a reasonable overall survival in patients with stage III NSCLC. However, less than half of the patients completed this regimen, and the additional effect of S-1 was marginal compared with historical control.

Conclusions: We concluded that chemoradiotherapy alone is still the recommended standard treatment for patients.

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1. Introduction

Lung cancer remains the leading cause of cancer related deaths worldwide.[1] Non-small-cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases and approximately 30% of patients have locally advanced lung cancer.[2] The standard treatment for locally advanced NSCLC patients involves concurrent thoracic radiotherapy (TRT) and chemotherapy.[3]

A treatment regimen has been developed in Japan using cisplatin and vinorelbine concurrently administered with thoracic radiotherapy at a total dose of 60 Gy to patients with locally advanced NSCLC.[4,5] To improve survival, docetaxel consolidation therapy is conducted following the same regimens administered to NSCLC patients.[6] This is based on the concept of clinical trial SWOG 9504[7] that suggested that consolidation chemotherapy was a promising strategy for the treatment to NSCLC patients. However, a drawback is the fact that a majority of the patients in the Japanese study were not able to continue with the consolidation of docetaxel due to treatment related pneumonitis.[6]

S-1 is an oral fluoropyrimidine agent designed to enhance anticancer activity and reduce toxicity through the combined use of an oral fluoropyrimidine agent (tegafur), a dihydropyrimidine dehydrogenase inhibitor (5-chloro-2,4-dihydroxypyridine) and an orotate phosphoribosyl transferase inhibitor.[8] S-1 was shown to produce active response as a single agent for metastatic NSCLC with minimal toxicity.[9] S-1 has been launched for use as an adjuvant therapy for early stage lung cancer,[10] chemoradiotherapy for stage III,[11] frontline chemotherapy[12] and 2nd or 3rd[13] line chemotherapy in advanced stages of the disease.

Based on a promising efficacy with S-1, we hypothesised that chemoradiotherapy followed by S-1 consolidation would be feasible and clinically active. Hence, the Japan National Hospital Organization Study Group for Lung Cancer (JNHOSGLC) conducted a multicentre, phase II study for patients with unresectable stage III NSCLC, where chemoradiotherapy was administered to patients followed by S-1 consolidation therapy (UMIN000002381). The primary objective was to determine the response rate, while secondary objectives were to determine the safety of this new regimen and to estimate progression-free and overall survival.

2. Patients and methods

2.1. Eligibility criteria

Patients with histologically or cytologically confirmed NSCLC at unresectable stage III disease were eligible for this study. Stage III was decided based on the 6th AJCC Cancer Staging Manual.[14] Eligible stage IIIA disease was defined by the presence of multiple and/or bulky N2 mediastinal lymph nodes on computed tomography (CT). Eligible stage IIIB disease was assigned either by N3 (contralateral mediastinal) or by T4 from invasion of mediastinal structures, heart, great vessels, trachea, carina, oesophagus or vertebral body. Confirmation of T4 or N3 status was established according to T4 involvement found at the time of thoracotomy or thoracoscopy; involvement of the trachea or carina by bronchoscopy; unequivocal invasion of the heart, oesophagus, aorta or vertebral body by CT scan, or magnetic resonance imaging; or biopsy of contralateral mediastinal N3 nodes. Eligible patients also needed to meet the following criteria: measurable disease of 20 mm or more in size; no prior history of chemotherapy or TRT; Eastern Cooperative Oncology Group performance status of 0 or 1; aged between 20 and 74 years; have leucocytes $\geqslant$ 4000/mL, platelets $\geqslant$ 100,000/mL, and haemoglobin $\geqslant$ 9.5 g/dL, serum creatinine < institutional upper limit of normal, and partial pressure of arterial oxygen $\geqslant$ 70 mmHg. Patients were excluded if they had infections; apparent interstitial pneumonitis or fibrosis on chest CT; irradiation field larger than half of an ipsilateral lung; severe complications; another active cancer. The ethics committee of each participating institution approved the protocol, and all patients provided written informed consent before the start of the study. For staging, all patients underwent CT of the thorax and abdomen, and either a brain CT scan or magnetic resonance imaging (MRI). A radio isotopic bone scan was also performed for all patients. Positron emission tomography was not necessary for enrolment.

2.2. Therapy

Treatment consisted of a chemoradiotherapy phase with two cycles of cisplatin and vinorelbine followed by a consolidation phase with two cycles of S-1. Chemoradiotherapy consisted of cisplatin at 80 mg/m^2 on days 1 and 29; vinorelbine at 20 mg/m^2 on days 1, 8, 29 and 36; and concurrent TRT at a total dose of 60 Gy. Sequential S-1 consolidation therapy at doses of 80-120 mg/body twice per day was started on day 57 with two cycles of 4 weeks administration and 2 weeks withdrawal. The dose of S-1 was determined based on body surface area (BSA): 80 mg was delivered when BSA was less than 1.25/m^2, 100 mg when 1.25/m^2 < BSA < 1.50/m^2 and 120 mg when BSA $\geqslant$ 1.50 m^2.

Concurrent TRT began on day 2 of chemotherapy by using a linear accelerator (6–10 megavolt), in 2-Gy, single and daily fractions for five consecutive days per week to provide a total dose of 60 Gy. A curative radiation field was constructed by using a plain chest radiograph and a contrast-enhanced computed tomography (CT) scan. The initial dose (approximately 40 Gy) was administered to the primary tumour, the ipsilateral hilum with a 2-cm margin, and involved mediastinal lymph nodes with a 1-cm margin. Prophylactic radiation fields were not planned except for subcarinal lymph nodes. Subsequently, a 20-Gy dose was given as a booster in accordance with tumour shrinkage. An initial TRT dose of 40 Gy was administered to the antero-posterior parallel–opposed pair of portals. Oblique anterior and posterior fields were required to avoid over dosage of the spinal cord.

The criteria for starting consolidation chemotherapy included completion of two cycles of cisplatin and vinorelbine, a full dose of thoracic radiotherapy, and the absence of a progressive disease, as well as being in good general condition.

2.3. Evaluation

All eligible patients who received treatment were considered assessable for response and toxicity measures. Chest X-rays,

blood counts and blood chemistry studies were repeated once a week during the treatment period. Follow-up studies including CT scan were performed once a month during the treatment period and every 3 months after treatment. The response was evaluated in accordance with Response Evaluation Criteria in Solid Tumours (RECIST). For evaluation of the antitumour effects, an extramural review was conducted. Acute toxicity was graded according to the NCI Common Toxicity ver. 3.0.

2.4. Statistical methods

We calculated the sample size based on Fleming's single-stage design for phase II study. We set a response rate of 60% as a baseline survival rate and 75% as the high level of interest with a power of 0.8 at a one-sided significance level of .05, requiring an accrual of at least 62 eligible patients. Assuming the loss of follow-up cases, a minimum of 65 patients was required for this study. Progression-free and overall survival was estimated using the Kaplan–Meier method, with corresponding two-sided 95% confidence interval (CI) for median times. For progression-free survival, follow-up measures were conducted during the study enrolment to document evidence of disease progression or death, or last documented progression-free status. Overall survival was measured from the study enrolment to the date of death or last contact. Statistical analyses were performed with SAS version 9.2 software (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

Sixty-six patients were enrolled between January 2006 and July 2009. One patient that did not receive any protocol treatment was not assessable and therefore not included in the analysis. Baseline patient characteristics and demographics are listed in Table 1. The median age was 63 years (range, 45–73 years), and 55 patients were male and 10 patients were female. Thirty patients (46%) were at stage IIIA and 35 patients (54%) were at stage IIIB. Histological studies showed squamous cell carcinoma in 33 patients, adenocarcinoma in 23 patients and other cancers in nine patients.

3.2. Treatment delivery

Of the 65 patients, 57 patients (87.7%) completed the concurrent portion of the regimen. Failure to complete the concurrent therapy was due to toxicities such as grade 3 pneumonitis ($n = 1$) and ileus ($n = 1$), delay in chemotherapy for more than 2 weeks ($n = 3$), pneumonia ($n = 1$), deteriorating condition ($n = 1$) and surgery ($n = 1$). Forty-five patients (69.2%) proceeded to consolidation therapy. Reasons for failing to proceed to consolidation therapy included chemoradiotherapy toxicities such as persistent neutropenia ($n = 2$) and renal failure ($n = 2$), pneumonia ($n = 1$) declining performance status ($n = 1$), cardiac ischaemia unrelated to the treatment ($n = 1$), progressive disease documented on restaging after completion of the concurrent therapy ($n = 1$), vertigo ($n = 1$), refusal to undergo consolidation therapy ($n = 1$) and surgery ($n = 1$). A total of 31 patients (47.6%) completed the two cycles of consolidation therapy. Early discontinuation of the consolidation therapy included toxicity of more than grade 2 pneumonitis ($n = 9$), declining performance status ($n = 1$), disease progression ($n = 2$), cerebral infarction unrelated to the treatment ($n = 1$) and refusal of the therapy ($n = 1$).

3.3. Response and survival

The overall response rate during the study was 61.5% (95% CI, 48.6–73.3%) with one complete response and 39 partial responses. Stable disease and progressive disease occurred in 19 patients (29.2%) and six patients (9.2%), respectively. One patient had an inadequate reassessment. The estimated median progression-free survival was 10.2 months (95% CI, 8.6–13.7 Fig. 1). Kaplan–Meier estimates of progression-free survival were 44.6% (95% CI, 32.1–57.1%) at one year and 17.9% (95% CI, 6.3–29.5%) at three years. The estimated median duration of survival in all patients was 21.8 months (95% CI, 15.6–27.6; Fig. 2). Twenty-three patients remained alive after a median follow-up of 37.7 months (range, 12.5–54.3 months). Kaplan–Meier estimates of overall survival were 73.9% (95% CI, 63.2–84.5%) at one year and 34.0% (95% CI, 21.2–46.9%) at three years.

3.4. Toxicity

Grade 3 or 4 toxicities for the concurrent treatment phase are summarised in Table 2. Among the 65 assessable patients, one patient had a grade 3 pneumonitis (1.5%) while there were no grade 3 or 4 treatment-associated oesophagitis. The most common grade 3 or 4 haematological toxicities were leukopaenia (56.8%) and neutropenia (53.7%).

Table 3 summarises the grade 3 or 4 toxicities for the 44 patients who received consolidation therapy. It is apparent that minimal toxicity was observed in patients who received consolidation therapy. The most common grade 3 or 4 toxicity was anaemia (8.9%). Leukopaenia or neutropenia was observed in just three patients (6.7%) and severe oesophagitis was not observed. Seven patients developed grade 2 pneumonitis and two grade 3 pneumonitis during consolidation therapy. One patient died three months after chemoradiotherapy as the result of pneumonitis.

4. Discussion

This is the first phase II study to investigate the use of the oral fluoropyrimidine agent S-1 as a consolidation drug after chemoradiotherapy in stage III NSCLC. Our data indicated a reasonable survival with a median survival time (MST) of 21.8 months and a three-year survival rate of 34.0%. In addition, tumour response was demonstrated to be 61.5% and clinically active. However, less than half of the patients completed this regimen (47.6%) and it is unlikely that this treatment is feasible.

This study was originally designed to extend and enhance the concept of consolidation as reported in SWOG 9504,[7] a phase II study, where docetaxel was administered after cisplatin, etoposide (PE) and TRT to patients with stage III

NSCLC. Although a significant MST of 26 months was observed in that study, this finding could not be replicated in a phase III study. Dr. Hanna and colleagues reported that consolidation with docetaxel after PE and TRT could not improve survival compared with chemoradiotherapy alone with the same MST range of 23 months in each arm.[15]

Previous studies in Japan showed that chemoradiotherapy using cisplatin and vinorelbine elicits high response and survival rates in patients with stage III NSCLC. A phase I study showed an MST of 30.4 months with a three-year survival rate of 50% in 18 patients.[4] A retrospective study using the recommended dose demonstrated an MST of 21 months and a three year survival rate of 33% in 73 patients, where the chemotherapy cycle was originally planned with a maximum of three cycles but with a median of two (mean 2.4, ranges 1–3).[5] Our treatment regimen was also designed based on the aforementioned phase I trial and is almost identical to that of the retrospective study with the exception of using consolidation S-1, and the results indicated an MST of 21.8 months and a three-year survival rate of 35%. Considering the retrospective study as a historical control, the comparable survival data between the two studies suggest that the effect of S-1 consolidation is marginal and unclear. Although a phase III trial is needed to conclude the benefit of consolidation of S-1, different administrative methods for the drug may be more appropriate to patients with stage III NSCLC, as chemoradiotherapy including cisplatin and S-1 was reported to be active and promising.[11]

Table 1 – Patient Characteristics (*N* = 65).

	No. of patients	%
Gender		
Male	55	84.6
Female	10	15.4
Age, years		
Median	63	
Range	45–73	
Performance status		
0	27	41.5
1	38	58.5
Stage		
IIIA	30	46.2
IIIB	35	53.8
Histology		
Squamous cell	33	50.7
Adenocarcinoma	23	35.4
Large cell	2	3.1
Other	7	10.8

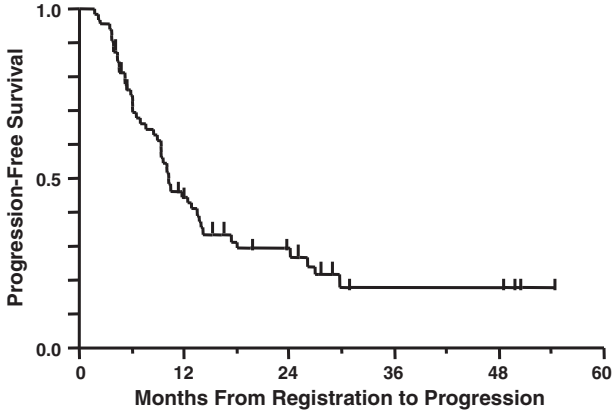

Fig. 1 – Progression-free survival of patients treated with cisplatin + vinorelbine + concurrent thoracic radiotherapy followed by S-1.

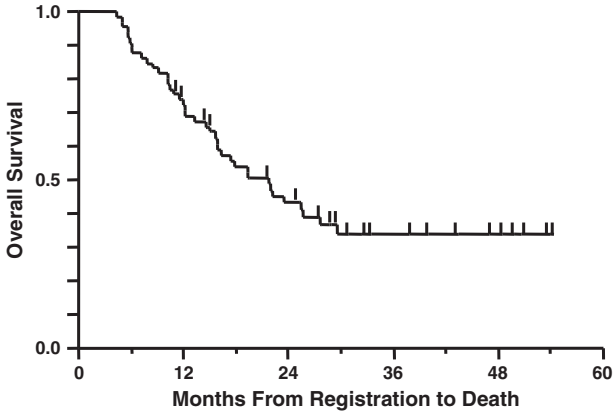

Fig. 2 – Overall survival of patients treated with cisplatin + vinorelbine + concurrent thoracic radiotherapy followed by S-1.

Cisplatin, vindesine, and mytomicin (MVP) were used for chemoradiotherapy in patients with stage III NSCLC in other studies, which is a preceding regimen of cisplatin and vinorelbine. In a phase III study of WJTOG 0105,[16] the standard treatment arm of MVP and concurrent TRT yielded an MST of 20.5 months with four cycles of chemotherapy. In another phase III trial in Japan,[17] the same regimens produced an MST of 23.7 months with two cycles of chemotherapy. Although the difference in MST may come from a split form of radiotherapy delivery in the WJTOG study, no survival benefits were observed from the addition of two cycles of chemotherapy. Again, these results are consistent with our finding that the effect of consolidation is marginal.

Feasibility is another problem in this study. Although 57 patients (87.7%) completed the concurrent portion of the regimen, only 31 patients (47.6%) finished the consolidation phase. Nine developed grade 2 or 3 pneumonitis in the 45 patients during the S-1 consolidation. In previous study, docetaxel consolidation following cisplatin, vinorelbine and TRT was reported as not feasible in Japanese patients. Almost the same 86% completed chemoradiotherapy, however, 34 patients (37%) finished consolidation therapy, whereas 14 of the 25 patients that participated in the consolidation phase developed pneumonitis.[6] On the other hand, in the aforementioned SWOG 9504, 74 patients (88%) completed chemoradiotherapy and 49 patients (59%) finished consolidation. An ethnic difference has been suggested in toxicity in NSCLC patients[18] and it is possible that pneumonitis is more common in Japanese compared to Caucasian, and further research will be required. In haematological toxicities in our study, the incidence of grade 3 or 4 neutropenia and leukopaenia were 53.7% and 56.8%, respectively, which is similar to previous reports.[5] Considering other side effects, a lower incidence of oesophagitis was

Table 2 – Major toxicities, chemoradiotherapy (*N* = 65).

	Grade 3		Grade 4	
	No.	%	No.	%
Haematologic				
Leukopaenia	27	41.5	10	15.3
Neutropenia	25	38.4	10	15.3
Anaemia	3	4.6	2	3.0
Thrombocytopenia	0	0.0	0	0.0
Neutropenic fever	4	6.1	0	0.0
Nonhaematologic				
Nausea	2	3.0	0	0.0
Vomiting	0	0.0	0	0.0
Anorexia	2	3.0	0	0.0
Oesophagitis	0	0.0	0	0.0
Pneumonitis	1	1.5	0	0.0

Table 3 – Major toxicities, consolidationl S-1 (*N* = 45).

	Grade 3		Grade 4	
	No.	%	No.	%
Haematologic				
Leukopaenia	2	4.4	0	0.0
Neutropenia	1	2.2	0	0.0
Anaemia	3	6.7	1	2.2
Thrombocytopenia	0	0.0	0	0.0
Neutropenic fever	0	0.0	1	2.2
Nonhaematologic				
Nausea	0	0.0	0	0.0
Vomiting	0	0.0	0	0.0
Anorexia	0	0.0	0	0.0
Oesophagitis	0	0.0	0	0.0
Pneumonitis	2	4.4	0	0.0

observed in our study. Severe radiation-related oesophagitis usually occurred in concurrent chemoradiotherapy and the incidences were reported to be in the range of 17–28%.[15,19] However, there have been several reports that minimal side-effects of oesophagitis were seen in the regimes using vinca alkaloids[5,16,17] and including ours, and further study is needed to confirm this association.

In conclusion, chemoradiotherapy with cisplatin and vinorelbine followed by S-1 consolidation demonstrated a reasonable overall survival in patients with stage III NSCLC. However, considering the questionable feasibility and marginal additional effect of S-1, it is recommended that chemoradiotherapy alone is still the standard patient treatment.

Conflict of interest statement

None declared.

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