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ORIGINAL ARTICLE

Concurrent chemoradiotherapy using cisplatin and S-1, followed by surgery for stage II/IIIA non-small cell lung cancer

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Abstract

Objectives Because chemoradiotherapy using cisplatin and S-1, an oral fluoropyrimidine, is effective for unresectable non-small cell lung cancer (NSCLC), an induction setting was used in a multicenter phase II study (Clinical trial number: UMIN000008205). The correlations of relapse and clinicopathological factors were analyzed.

Methods We defined locally advanced NSCLC as pathologically proven chest wall invasion or hilar and/or mediastinal lymph node metastases by endobronchial ultrasound-guided transbronchial needle aspiration. The patients received two courses of S-1 administration for 14 days and intravenous cisplatin injection on day 8. A total dose of 40 Gy radiotherapy was concurrently received. Surgical resection was performed after completion of the treatment.

Results Of the 23 eligible patients, 18 had stage IIIA and 5 had stage IIB NSCLC. Twenty of the eligible patients (87.0%) completed the regimen. Six (26.1%) complete responses were identified and 12 cases (52.2%) were histopathologically downstaged by induction chemoradiotherapy (ICRT). The 3-year overall survival rate was 58.1% and relapse-free survival (RFS) rate was 52.0%, respectively. Among several clinicopathological parameters, univariate RFS analysis identified that only downstaging was significantly associated with longer RFS times ($p=0.003$). The radiological response did not reflect pathological response. When the variables of preoperative pathologically proven N2 metastasis, pathological ICRT effectiveness, and downstaging were included in the Cox proportional hazard modes, only the parameter of downstaging displayed significant hazard ratio (hazard ratio 0.13, $p=0.010$).

Conclusion This protocol is considered an option among preoperative therapies and has obvious benefits for pathologically downstaged cases.

Clinical trial number UMIN000008205.

Trial registration date June 19, 2012.

Keywords Induction chemoradiotherapy · S-1 · Relapse · Downstaging · Non-small cell lung cancer

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Introduction

Lung cancer remains the leading cause of cancer-related deaths worldwide [1]. Despite the development of higher-resolution chest imaging techniques, many of the diagnosed patients were in advanced stage of disease [2]. In the latest National Comprehensive Cancer Network (NCCN) guidelines for NSCLC, preoperative chemoradiotherapy (CRT) is given as a treatment option for patients that are likely to receive adjuvant chemotherapy after surgical evaluation.

S-1 is a novel oral fluoropyrimidine derivative consisting of tegafur (FT) and two modulators: 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) [3]. FT is a prodrug of 5-fluorouracil (5-FU). CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase, an enzyme involved in the degradation of 5-FU. Oxo is a reversible competitive inhibitor of orotate phosphoribosyltransferase, which reduces GI toxicity caused by 5-FU [4]. S-1 has been shown to have one of the highest levels of response as a single agent for NSCLC [5]. For the patients with non-resectable stage III NSCLC, concurrent radiotherapy with S-1 plus cisplatin has been proposed. Objective response rates for NSCLC were 77–87.5% [6–8].

Given the high response rates, mild toxicities, and good survival rates of CRT with S-1 and cisplatin for advanced NSCLC, which is comparable with the standard regimens of CRT using cisplatin and etoposide, vinorelbine, or pemetrexed, we conducted a feasibility study of preoperative induction chemoradiotherapy (ICRT) using cisplatin and S-1 for stage II/IIIA NSCLC in a multi-center phase II clinical trial. Previously, we have reported high completion rates and mild adverse reactions of the regimen [9]. In the present study, we analyzed the prognostic outcomes and the correlation with various clinicopathological factors including pathologically proven downstaging evaluated by preoperative lymph node biopsies and postoperative resected tissue samples.

Patients and methods

Patients

This trial was non-blinded and open label (Clinical trial number; UMIN000008205). The primary end point was the completion rate of the scheduled ICRT and surgery. Secondary end points were the response rate, incidence, and grade of adverse reactions. Patient eligibility required compliance with the following criteria: NSCLC with histological proof; pathological stage II or IIIA NSCLC (according to the 7th edition of UICC/AJCC, 2010) [2]; no prior treatment; age > 20 and < 80 years, with sufficient oral intake; and performance status (PS) 0 or 1. Patients also needed adequate organ function. Patients with a history of drug hypersensitivity, serious surgical or non-surgical complications, or active secondary cancer were excluded. Mediastinal lymph node metastases were pathologically diagnosed using EBUS-TBNA before ICRT.

Treatment protocol

Chemotherapy comprised two courses (2 weeks administration, 2 weeks withdrawal) of cisplatin at 60 mg/m^2 and S-1 (FT, gineracil, oteracil potassium; Taiho Pharmaceutical, Tokyo, Japan) at 80–120 mg/body/day according to the body surface area (BSA). Cisplatin was administered at day 8 in the course and S-1 was administered orally, twice daily after meals. Thoracic radiotherapy was started on day 1 of the first cycle of chemotherapy. Radiotherapy was directed to the planning target volume (PTV) with a leaf margin of 0.5 cm for a total dose of 40 Gy/20 fractions/4 weeks.

The preoperative staging was decided by the CT image analysis after the ICRT. Within 2 weeks after completing the ICRT, the patients were assessed for their response to the induction therapy by CT scan and were restaged. If disease control, such as a complete response, partial response, or stable disease, was achieved, a curative-intent resection was planned 4–6 weeks after completion of the ICRT.

Evaluation of the response

The response was evaluated in accordance with the New Response Evaluation Criteria in Solid Tumors guidelines, Version 1.1 [10]. Histological analysis of the tumor was based on the World Health Organization classification for cell types. Postoperative pathological response to ICRT was evaluated by Ef (Ef1a: ≥ 2/3 viable tumor cells; Ef2: < 1/3 viable tumor cells; and Ef3: no viable tumor cells in resected specimens).

Study design and statistical analysis

The number of patients to be enrolled in this study was calculated as 23, with the prospect of some incomplete cases. In another reported phase II study of S-1, cisplatin, and radiotherapy for locally advanced NSCLC, 48 of 50 patients completed the four courses of chemotherapy with a completion rate of 96% [7]. Assuming a completion rate of 80% in our study, with a planned eligible sample size of 19 patients, the 90% confidence interval (CI) for the completion rate was estimated to range from 65 to 95%. This 80% completion rate means that 80% of patients would complete both planned ICRT and surgery.

The Kaplan–Meier method was used to estimate the time-to-event functions of OS and RFS. The log-rank test was used to test for possible differences between estimated time-to-event curves. The prognostic relevance of a single factor was determined by multivariate Cox regression analysis. Variables that were associated with survival ($p < 0.3$) on univariate analysis were included in the multivariate analysis. The Chi-square test was used to analyze associations between relapse and clinicopathological factors. A p value of 0.05 was considered statistically significant, and all comparisons were 2-sided. JMP 13.0 statistical software (SAS, Cary, N.C., USA) was used to perform all analyses.

Ethics

This study was approved by the institutional review board at each site. Patients decided whether or not they would participate in the trial after being given a detailed explanation, and written informed consent was obtained from all patients prior to enrollment.

Results

Patient characteristics

A total of 23 patients were initially enrolled in the present study. Table 1 shows the characteristics of the 20 patients who completed two courses of chemotherapy with 40 Gy of concurrent radiotherapy and underwent surgical resection (completion rate 87.0%; 90% CI 74.7–99.3%). The median age of the patients was 64 years (range 37–73 years). All patients showed a performance status of 0. Complete resection was performed in all 20 surgically resected patients including 12 cases of lobectomy, two cases of bilobectomy and six cases of lobectomy with chest wall resection.

Image assessment and pathological therapeutic efficacy

After receiving the ICRT, therapeutic efficacy was evaluated by CT image before operation. Seven (35%) of the 20 patients achieved a partial response (PR), and stable disease (SD) was observed in 13 patients (65%). Pathological findings revealed that all cases were curatively resected. There were seven (35%) pathological complete responses (Ef3: no viable tumor cells in resected specimens), and some pathological response was recognized in all of the remaining patients. Accordingly, 13 cases (65%) were pathologically downstaged by ICRT. The Ef1/2 downstaged cases (four cases) were all N-factor-based downstaging, suggesting E-BUS/TBNA-proved malignant cells were killed by ICRT in those cases. Interestingly, 13 radiological SD cases included eight pathologically downstaged cases, suggesting that radiological examination could not be reflected by pathological responses.

Table 1 Correlation of various clinicopathological factors with relapse in 20 patients who completed the therapy

Parameter	*n*	Relapse (−)	Relapse (+)	*p* value
Age (years)				
< 63	9	6	3	0.670
≥ 64	11	6	5	
Gender				
Male	18	11	7	1.000
Female	2	1	1	
Histologic type				
Adenocarcinoma	10	6	4	1.000
Non-adenocarcinoma	10	6	4	
Preoperative pathologically proven N2 metastasis				
Absent	7	6	1	0.158
Present	13	6	7	
T3/T4 disease				
Absent	9	5	4	1.000
Present	11	7	4	
Radiological ICRT effectiveness				
Stable disease	13	8	5	1.000
Partial response	7	4	3	
Pathological ICRT effectiveness				
Ef1/2	13	6	7	0.158
Ef3	7	6	1	
Downstage				
Absent	7	1	6	0.004*
Present	13	11	2	

ICRT induction chemoradiotherapy, *Ef* effect

*Statistically significant as evaluated by Chi-square test

Correlation of clinicopathological factors with relapse

Table 1 shows the correlation of clinicopathological factors with relapse. Chi-square analysis of the data of these 20 patients indicated that downstaging was significantly correlated with low incidence of relapse ($p = 0.004$). Multivariate analysis also represented that the odds ratio of downstaging was significantly low (Table 2, Odds ratio 0.04, $p = 0.019$), but not changed by other parameters.

Survival analysis

The 3-year overall survival rate was 58.1% and relapse-free survival (RFS) rate was 52.0%, respectively (Fig. 1). Table 3 lists the 3-year RFS rates according to clinicopathological features. Among several clinicopathological parameters,

Table 2 Logistic regression analysis for relapse in 20 patients who completed the therapy

Parameter	Feature	Odds ratio	95% CI	*p* value
Preoperative pathologically proven N2 metastasis	Present	3.36	0.12–96.81	0.480
Pathological ICRT effectiveness	Ef3	0.30	0.01–8.58	0.480
Downstage	Present	0.04	0.002–0.59	0.019*

ICRT induction chemoradiotherapy, *Ef* effect

*Statistically significant

univariate RFS analysis identified that only downstaging was significantly associated with longer RFS times (Fig. 1, $p=0.003$). When the variables of preoperative pathologically proven N2 metastasis, pathological ICRT effectiveness, and downstaging were included in the Cox proportional hazard modes, only the parameter of downstaging displayed significant hazard ratio (Table 3, hazard ratio 0.13, $p=0.010$) (Fig. 2).

Discussion

The standard regimen of ICRT for NSCLC is platinum doublet and concurrent radiotherapy. In the regimen, 40–60 Gy radiation and chemotherapy with cisplatin and etoposide, veinorelbine, or pemetrexed are normally selected. We have previously shown that S-1 plus cisplatin with concurrent radiotherapy followed by surgery is a feasible and promising treatment for stage II/IIIA NSCLC in a prospective study [9]. The completion rate for the planned courses of ICRT was 87.0%, which compares favorably with the chemotherapy compliance seen in other ICRT trials [11, 12]. Toxicity was low. Significantly, hair loss, renal dysfunction, or vasculitis, which is often observed in the standard regimen, was not observed. No grade 4 adverse reactions were observed throughout the ICRT.

In the present analysis, we reported high 3-year OS and RFS rates of 58.1% and 52%, which were comparable to those of previously reported trials [13, 14]. Although the exact mechanisms of the high efficacy of this regimen in an ICRT setting remain unclear, there are significant advantages in the combination of S-1 and cisplatin with radiotherapy. First, cisplatin and fluoropyrimidine are both radiation sensitizers [15–17]. CDHP in S-1 also has a radiosensitizing effect [18]. Furthermore, cisplatin is known to be a biochemical modulator of 5-FU [19, 20]. Therefore, the effects of

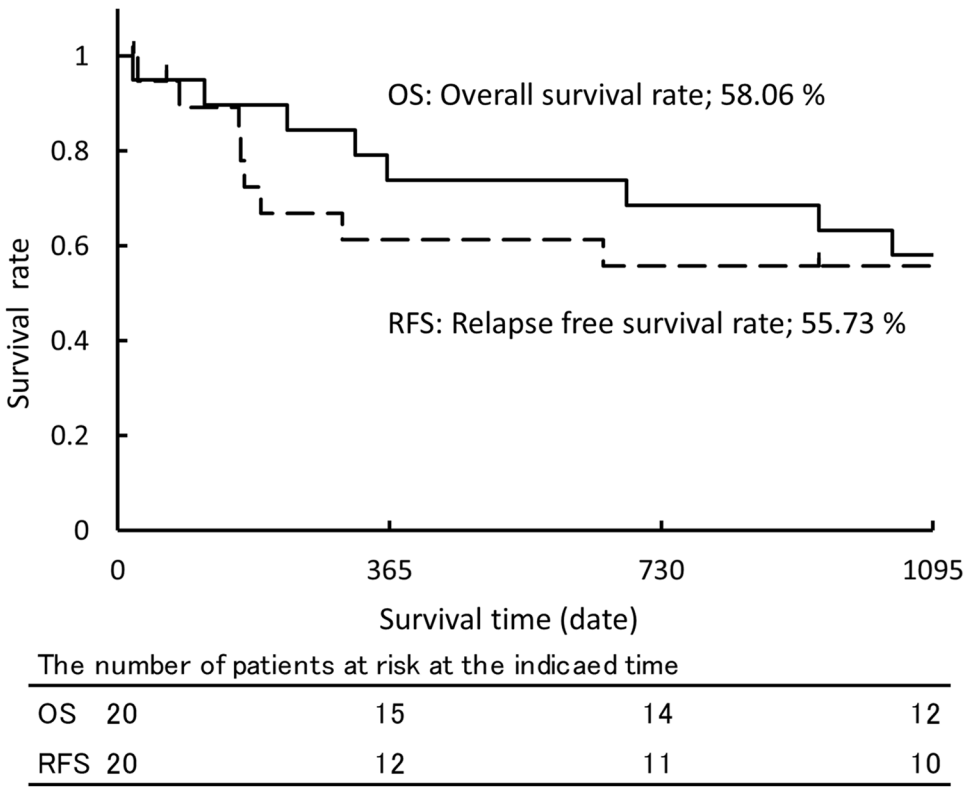

Fig. 1 Kaplan–Meier analysis of overall and relapse-free survival of patients who were treated with chemoradiotherapy using cisplatin and S-1, followed by surgery for stage II/IIIA NSCLC

Table 3 Univariate and multivariate RFS analysis according to clinicopathological features in 20 patients who completed the therapy

Parameter	No. of patients	Univariate analysis		Multivariate analysis	
		% 3-year survival	*p* value	Hazard ratio (95% CI)	*p* value
Age (years)					
< 63	9	57.14	0.896		
≥ 64	11	54.55			
Gender					
Male	10	56.47	0.970		
Female	2	50			
Histologic type					
Adenocarcinoma	10	60	0.572		
Non-adenocarcinoma	10	50			
Preoperative pathologically proven N2 metastasis					
Absent	7	80	0.204	N2 metastasis; 1.97 (0.33–37.64)	0.500
Present	13	46.15			
T3/T4 disease					
Absent	9	55.56	0.773		
Present	11	56.25			
Radiological ICRT effectiveness					
Stable disease	13	58.33	0.676		
Peartial response	7	50			
Pahological ICRT effectiveness					
Ef1/2	13	46.15	0.185	Ef3; 0.40 (0.02–2.34)	0.347
Ef3	7	80			
Downstage					
Absent	7	14.29	0.003*	Downstage; 0.13 (0.02–0.62)	0.010*
Present	13	82.5			

ICRT induction chemoradiotherapy, *Ef* effect

*Statistically significant as evaluated by log-rank test and multivariate cox propotional hazard analysis

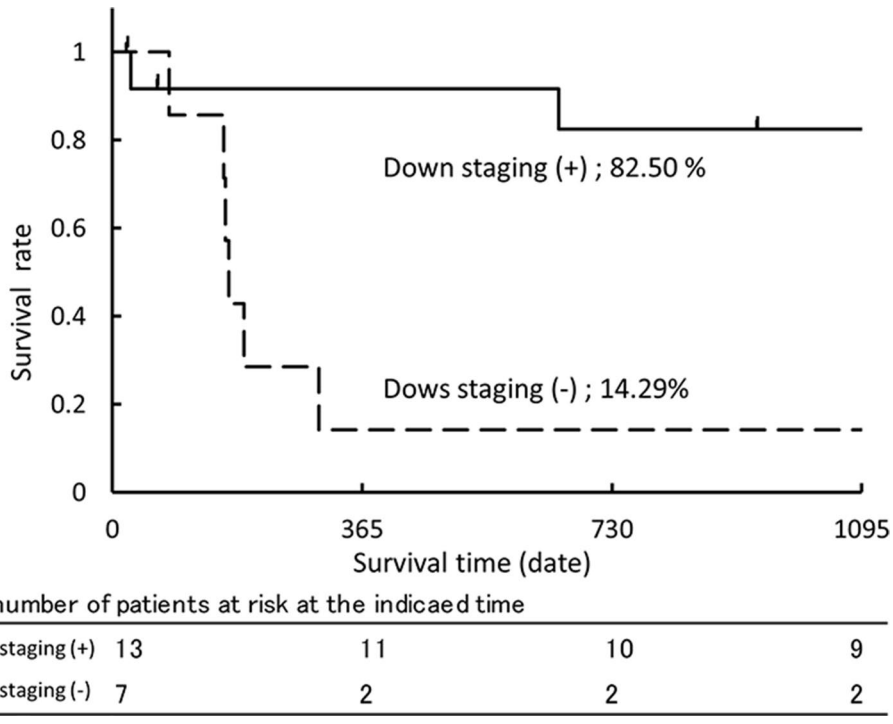

Fig. 2 Kaplan–Meier analysis of relapse-free survival in patients who were downstaged and those who were not after induction chemoradiotherapy using cisplatin and S-1, followed by surgery for stage II/IIIA NSCLC. $p = 0.003$

each therapy might additively enhance the anti-cancer effect in this ICRT regimen.

The second major finding of the present study is that it identified possible significant associations between clinicopathological factors and relapse. Correlation analysis and survival analysis revealed that downstaging was significantly associated with low incidence of relapse and longer RFS times. In addition, pathologically downstaged cases were all N-factor-based downstaging, suggesting that the group with ICRT-responded lymph node metastasis might benefit from this regimen of ICRT. Conversely, adjuvant chemotherapy will be necessary for a low pathological response group. It was interesting that histological type was not associated with relapse. The result is consistent with a pooled analysis study of S-1 trials in NSCLC in which the response rate did not differ according to histological type and, therefore, S-1 can also be used to treat squamous cell carcinoma [21]. Because the efficacy of anticancer drugs correlates with tumor genetic condition, such as DNA excision repair protein ERCC-1 for CDDP response [22], thymidine synthase and a single-nucleotide polymorphism (SNP) of ATP-binding cassette protein C11 (ABCC11) for S-1 adjuvant setting effectiveness [23], detailed genetic analysis will be necessary to find out the prognostic factor of this therapy.

To evaluate accurate pathological downstaging, E-BUS/TBNA was used in the present study. Reports of histopathological confirmation of downstaging are rare [24]. In two studies, pathological complete response was 21–37.5%, while 45.8–56% had mediastinal downstaging [25, 26]. Our results are comparable to those of the reported studies. The accurate evaluation of lymph node metastasis before and after the treatment revealed that eight of 13 (61.5%) radiological stable cases were pathologically downstaged. Clinicians must be aware that radiological evaluation might underestimate the real effect of ICRT and it is not correlated with pathological response.

Conclusion

Induction treatment using S-1 plus cisplatin and concurrent radiotherapy followed by surgery is a feasible and promising new treatment modality for locally advanced NSCLC. Accurate evaluation of histopathological downstaging and survival analysis revealed sufficient anti-cancer effects for preoperative treatment, especially pathologically downstaged patients. The present findings suggest that it would be reasonable to follow up with a properly conducted phase III study.

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Compliance with ethical standards

Conflict of interest The authors have nothing to disclosure with regard to commercial support. The authors have no conflicts of interest.

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