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Efficacy of S-1 after pemetrexed in patients with non-small cell lung cancer: A retrospective multi-institutional analysis

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Abstract

Background: S-1 and pemetrexed (PEM) are key treatments for non-small cell lung cancer (NSCLC). However, the mechanism of anticancer activity of S-1 and PEM is similar. Cross-resistance between S-1 and PEM is of concern. This exploratory study was designed to evaluate the treatment effect of S-1 following PEM-containing treatment.

Methods: This retrospective study included patients with advanced (c-stage III or IV, UICC seventh edition) or recurrent NSCLC who received S-1 monotherapy following the failure of previous PEM-containing chemotherapy at six hospitals in Japan. The primary endpoint of the study was the overall response rate (ORR). The secondary endpoint was the disease control rate (DCR), time to treatment failure (TTF), progression-free survival (PFS), and overall survival (OS).

Results: A total of 53 NSCLC patients met the criteria for inclusion in the study. Forty-six patients had adenocarcinoma (88.7%) and no patients had squamous cell carcinoma. Thirty-one patients (58.5%) received the standard S-1 regimen and 18 patients (34.0%) received the modified S-1 regimen. ORR was 1.9% (95% confidence interval [CI]: 0.00%–10.1%). Median TTF, PFS, and OS were 65, 84, and 385 days, respectively.

Conclusions: Although there were several limitations in this study, the ORR of S-1 after PEM in patients with nonsquamous (non-SQ) NSCLC was low compared to the historical control. One of the options in the future might be to avoid S-1 treatment in PEM-treated patients who need tumor shrinkage.

KEYWORDS
cross-resistance, lung cancer, Pemetrexed, S-1

INTRODUCTION

S-1 and pemetrexed (PEM) are key antitumor drugs for the treatment of non-small cell lung cancer (NSCLC). PEM and

Trial registration: UMIN ID:000033374.

cisplatin (CDDP) have previously shown superior overall survival (OS) compared with gemcitabine and CDDP in treating nonsquamous (non-SQ) NSCLC patients, and PEM and platinum treatment is usually used for non-SQ NSCLC patients.[1] S-1 monotherapy showed noninferiority for OS compared with docetaxel (DTX) in NSCLC patients previously treated with platinum-based antineoplastic drugs containing treatment and is used for NSCLC as a standard treatment.[2] However, the mechanism of anticancer activity of S-1 and PEM appears to be similar. For example, both S-1 and PEM target thymidylate synthase (TS).[3] Because of this similarity, cross-resistance between S-1 and PEM is a concern. Several preclinical studies have indicated that elevation of TS expression after PEM treatment might be one of the causes of cross-resistance between S-1 and PEM.[4,5] TS expression level has been reported to be associated with response to both S-1 and in NSCLC in a clinical setting.[6,7] These preclinical data indicate the concern about resistance to PEM might indicate resistance to S-1 in a clinical setting. Moreover, although there have been several studies on S-1 for NSCLC,[2,8]unfortunately, studies on the treatment effect of S-1 after PEM in the clinical setting are limited. If a cross-resistance between S-1 and PEM exists, then S-1 should be avoided as a treatment after PEM for NSCLC. The aim of our study was therefore to evaluate the treatment effect of S-1 after PEM containing treatment.

METHODS

Patient selection

This retrospective study included patients with advanced (c-stage III or IV, Union for International Cancer Control [UICC] seventh edition) or recurrent NSCLC who received S-1 monotherapy following the failure or discontinuation of previous PEM containing chemotherapy at six institutions in Japan between April 2012 and March 2017.

The full analysis set (FAS) included patients who (i) were pathologically diagnosed with NSCLC, (ii) received S-1 monotherapy for more than 15 days, (iii) previously received three or less treatments prior to S-1, (iv) received PEM-containing treatment prior to S-1 and (v) had at least one target lesion. The electronic medical records were reviewed retrospectively.

Data collection

The following factors were collected from the electronic medical records: age, sex, pathology, smoking status, main medical histories, main comorbidities, epidermal growth factor receptor (EGFR) mutation status, anaplastic lymphoma kinase (ALK) fusion gene status, clinical stage (UICC seventh edition), Eastern Cooperative Oncology Group (ECOG) performance status (PS) at the date of S-1 administration, date of S-1 or PEM administration, medication method of S-1,

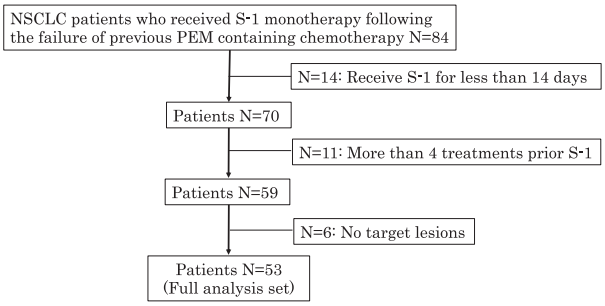

FIGURE 1 Scheme of full analysis set (FAS)

TABLE 1 Patient characteristics

All patients	53
Age, median (range)	70 (29-89)
Sex (%)	
Male	36 (67.9)
Female	17 (32.1)
PS (%)	
0	3 (5.7)
1	44 (83.0)
2	6 (11.3)
Smoking (%)	
No	13 (24.5)
Yes	40 (75.5)
Pathology (%)	
AD	47 (88.7)
SQ	0 (0)
Others	6 (11.3)
Staging (%)	
III	10 (18.9)
IV or relapse	43 (81.1)
EGFR mutation (%)	
No or unknown	46 (86.8)
Yes	7 (13.2)
Treatment schedule of S-1 (%)	
4W2R	31 (58.5)
2W1R	18 (34.0)
Others	4 (7.5)
Prior treatments before S-1 (%)	
1	11 (20.8)
2 or 3	42 (79.2)
Number of cycles of PEM (%)	
1∼4	29 (54.7)
5≤	24 (45.3)
Median period between last PEM administration and first S-1 administration (range)	118 days (11-625)
ICI between S-1 and PEM	none

number of treatment cycles, date of disease progression, date of final administration, survival information, date of last follow-up, and number of treatments prior to S-1.

Statistical analysis

This exploratory study was a multi-institutional retrospective observational study including six institutes in Japan. The primary endpoint was the overall response rate (ORR), which included partial response (PR) and complete response (CR). Secondary endpoints were disease control rate (DCR) which included CR, PR and stable disease (SD), time to treatment failure (TTF), progression-free survival (PFS), and OS. TTF was the number of days between the date of discontinuation of S-1 the date of the first day of S-1 monotherapy and PFS was the number of days between the date of the start of S-1 monotherapy and the date of disease progression or the date of death. OS was the number of days between the date of the start of S-1 monotherapy and the date of death. Tomita et al. previously reported that the ORR of S-1 was 9%.[9] This study was selected as a historical control because the cohort in this study was similar with this study (the efficacy of S-1 was evaluated retrospectively). On the other hand, PEM was not administered before S-1 in most cases in this cohort because the pharmaceutical approval of PEM occurred in 2009 in Japan (the therapy period of S-1 in the cohort was between March 2004 and October 2010 in the historical control). In this study, expected ORR was set to 9% if there was no cross-resistance between PEM and S-1 and an unacceptable ORR due to cross-resistance was set to 4%. Using the OneArm Binomial program (Cancer Research and Biostatistics, Seattle, WA, USA), 78 patients were needed to produce a stastical power of 80% with a one-sided type I error of 10%. If ORR had been less than 4%, then the confirmatory study was taken into consideration. DCR, median TTF, PFS and OS were also compared with the historical control. The Kaplan–Meier method was used to calculate TTF, PFS and OS. Tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[10] All statistical analyses were performed using EZR,[11] which is for R. More precisely, it is a modified version of R commander designed to add statistical function frequently used in biostatistics.

TABLE 2 Best response

Best response (%)	PR	1 (1.9)
	SD	21 (39.6)
	PD	31 (58.5)
ORR		1.9% (95% CI: 0.0%-10.1%)
DCR		41.5% (95% CI: 28.1%-55.9%)

Abbreviations: DCR, disease control rate; ORR, overall response rate.

RESULTS

The method of patient selection is shown in Figure 1. Fifty-three NSCLC patients met the criteria, and these patients were defined as the FAS.

The patient characteristics are shown in Table 1. Of the 53 patients, 26 patients (49.0%) were <70 years of age. Age, PS, smoking history, staging, and *EGFR* gene mutation status were similar to the historical control.[9] There were no patients with the *ALK* fusion gene. A total of 46 patients had adenocarcinoma (88.7%) and none of the patients had squamous cell carcinoma. Thirty-one patients (58.5%) received the standard S-1 treatment (administered for four weeks and the rest for two weeks) and 18 patients (34.0%) received the modified S-1 treatment (administered for two weeks and the rest for one week). Twenty-four patients received five or more PEM administrations. The median number of days between the last PEM administration and first S-1 administration was 118 (range: 11–625). No immune checkpoint inhibitors (ICIs) were administered between PEM and S-1.

The treatment efficacy of S-1 is shown in Table 2. ORR was 1.9% (95% confidence interval [CI]: 0.00%–10.1%) and DCR was 41.5% (95% CI: 28.1%–55.9%). This result met the

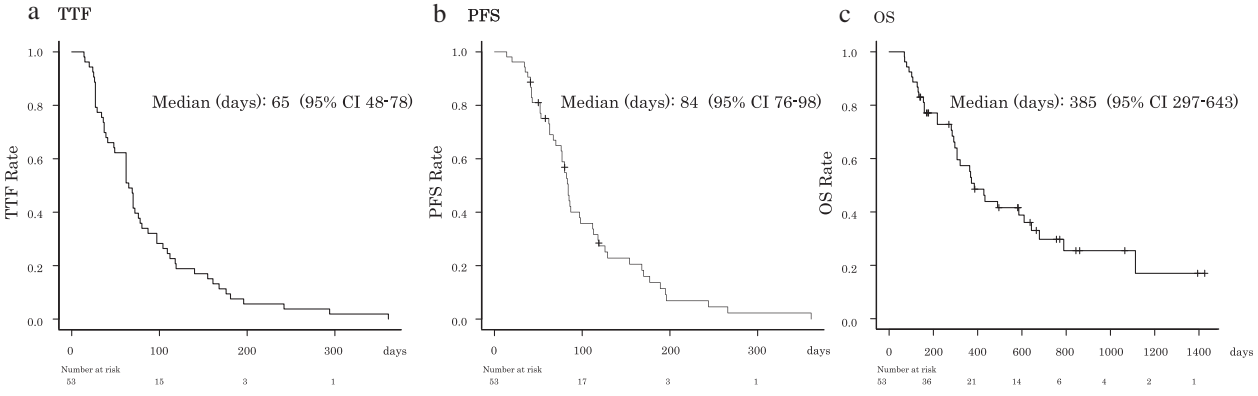

FIGURE 2 Kaplan–Meier curves of (a) treatment failure (TTF), (b) progression-free survival (PFS), and (b) overall survival (OS) for patients ($n = 53$) in the full analysis set

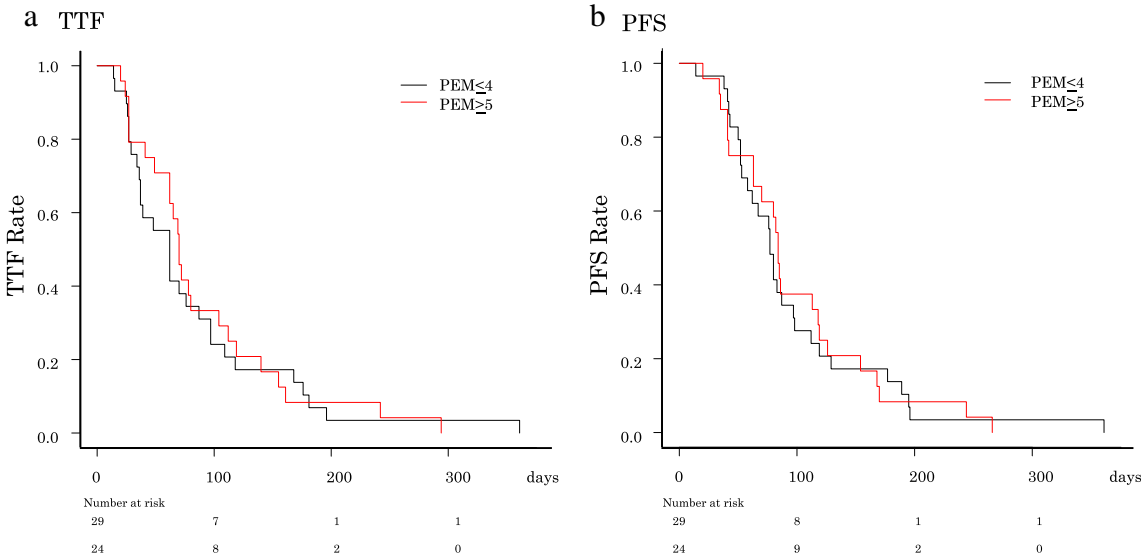

FIGURE 3 Kaplan–Meier curves of (a) treatment failure (TTF), (b) progression-free survival (PFS) stratified by the number of pemextred (PEM) administration. The black line indicates that subgroup PEM was administered four or less (PEM ≤ 4) and the red line indicates five or more (PEM ≥ 5). There was no significant difference between the PEM ≤ 4 group and PEM ≥ 5 in median TTF (77 days vs. 84 days, respectively; $p = 0.86$) and PFS (62 days vs 70 days, respectively; $p = 0.72$)

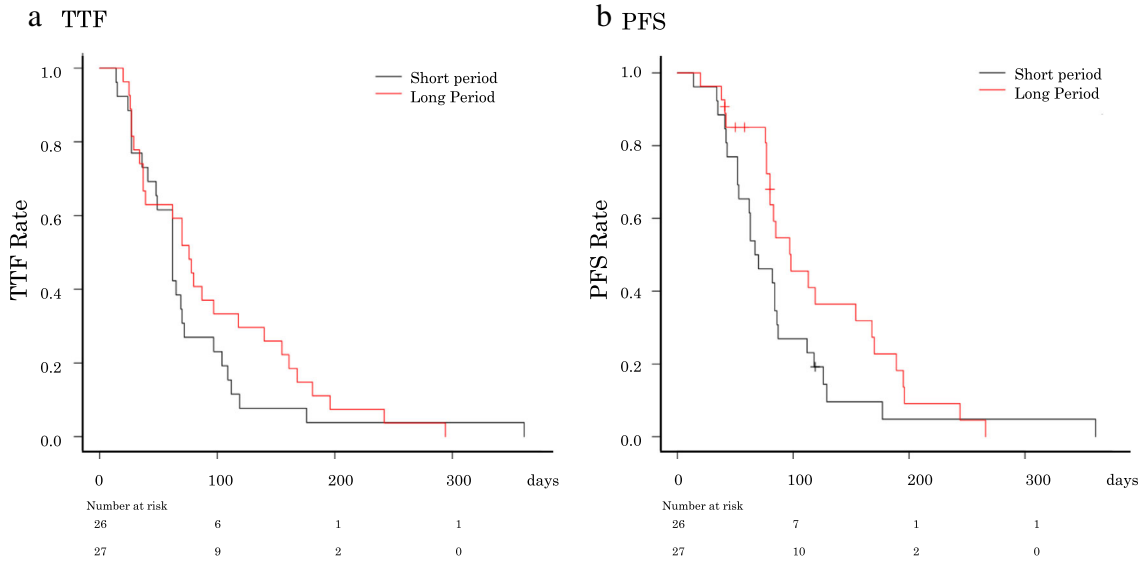

FIGURE 4 Kaplan–Meier curves of (a) treatment failure (TTF), (b) progression-free survival (PFS) stratified by the period between the last pemextred (PEM) and first S-1 administration. The black line indicates that for subgroup PEM the period was below the median (short period) and the red line indicates that it was above the median (long period). There was no significant defference between the short period group and long period group in median TTF (62 days vs. 76 days, respectively; $p = 0.29$) and PFS (68.5 days vs. 98 days, respectively; $p = 0.11$)

preplanned primary endpoint. It was suggested that the treatment efficacy of S-1 for NSCLC after PEM containing treatment might be less than no prior PEM containing treatment. Furthermore, in the historical control, especially in the non-SQ subset, ORR was 15.8% (95% CI: 3.3%–39.8%) and DCR was 57.8% (95% CI: 33.5%–79.7%).[9] The difference of ORR was higher in non-SQ.

Median TTF, PFS, and OS in this study were 65, 84, and 385 days, respectively (Figure 2). In the non-SQ subset of historical control, median PFS and OS were 4.2 months and 15.7 months, respectively (TTF not shown). Compared with the historical control, PFS and OS in this study tended to be worse.

To search for the predictive factor of efficacy of S-1 effect after PEM containing treatment, differential analysis was used for two factors. One was the number of PEM administrations and the other was the period between the last PEM administration and first S-1 administration. ORR was too low to analyze, TTF and PFS were used as a surrogate of efficacy. The differences in TTF and PFS between the

TABLE 3 Previous studies on S-1 monotherapy

Author	Year	Study design	Schedule[a]	Prior treatment number	Patient resistration period	Number of patients	Median age (y.o)	PS (0-1/2-4)	Pathology (AD/SQ/Others)	ORR (%)	DCR (%)	PFS (months)	OS (months)
Kawahara	2001	Phase II	4W/2W	0	Unknown	59	64	55/4	38/20/1	Total:22.0 AD:26.3 SQ:10.0	unknown	-	10.2
Totani	2009	Phase II	4W/2W	1	Aug 2005-July 2007	48	66.5	36/12	36/5/7	12.5	52	2.5	8.2
Govindan	2011	Phase II	2W/1W	1	Unknown	57	62	57/0	26/18/13	Total:7.1 Non-SQ:10.5 SQ:0	Totat:31 Non-SQ:60.5 SQ:44.4	2.9	7.3
Shiroyama	2011	Phase II	4W/2W	1⩽	June 2005-May 2007	44	64	44/0	30/11/3	13.6	77.3	4.2	16.4
Tomita[b]	2011	Retrospective	Physician's choice	1-3	Mar 2004-Oct 2010	19	Unknown	Unknown	19/0/0	15.8	57.9	Unknown	Unknown
Kasai	2016	Phase II	4W/2W	0	June 2007-June 2010	32	80	32/0	24/6/2	22.6	65.6	5.5	12.4
Nokihara	2017	Phase III	4W/2W	1,2	July 2010-June 2014	577	62	565/12	430/105/41	8.3	45.4	2.8	12.7
Tamura	2019	Retrospective	Physician's choice	1-10	Dec 2015-Aug 2017	Prior ICI: 21	60	19/2	17/4/0	20	46.7	3.0	Unknown
						No prior ICI: 23	62	20/1	14/9/0	17.6	58.8	2.6	Unknown
Imai	2020	Retrospective	Physician's choice	1-6	Jan 2005-Mar 2018	96	78	88/8	53/35/8	Total:8.3 AD:7.5 SQ:11.4	43.8	3.4	9.6
Yamamoto[c]	2020	Phase II	2W/1W	1-5	Aug 2016-Jul 2017	64	64	64/0	14/48/2	10.3	75.9	4.1	Unknown
Kato	2020	Retrospective	Physician's choice	1	Dec 2015-Jul 2017	Prior ICI: 49	67	35/12	23/26	6.1	38.8	1.9	7.9
						No prior ICI: 174	72	137/27	83/83/7	6.3	48.3	2.7	9.2
	present	Retrospective	Physician's choice	1-3	Apr. 2012-Mar. 2017	53	70	47/6	47/0/6	1.9	41.5	2.8	12.8

[a]4W2W: administration for four weeks and rest for two weeks.
[b]Adenocarcinoma subset analysis.
[c]Prior PEM containing treatment: 73.4%. Prior immune checkpoint inhibitor treatments: 76.6%.
Abbreviations: DCR, disease control rate: ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

two groups were assessed using a stratified log-rank test. As a result, both of two factors could not predict the efficacy of S-1 after PEM treatment (Figure 3, Figure 4). However, the longer period between last PEM and first S-1 group tended to lengthen PFS and TTF.

DISCUSSION

S-1 is the standard treatment for patients with previously treated NSCLC in a clinical setting.[2] However, ORR of S-1 after PEM in the present study seemed to have less antitumor effect than the historical control.

DCR, PFS and OS also showed similar tendencies, although the difference was modest. Banqu et al. previously reported a relationship between TS expression levels and the ability to develop resistance to antifolates using PEM resistant cell lines.[5] In addition, Takeda et al. reported immunohistochemical expression levels of TS and the response to treatment with S-1 in NSCLC. In the study comparing S1 plus carboplatin (SC group) with paclitaxel plus carboplatin (PC group), PFS of the low TS group tended to be longer than PFS of the high TS group in SC group, and there was no difference among the PC group.[6] Unfortunately, there have been no reports about evidence of elevated TS expression after PEM pretreatment in vitro or in clinical specimens. However, taking these reports into consideration, it has been postulated that one of the mechanisms of cross-resistance between PEM and S-1 is reduction of TS expression due to prior PEM treatment. Previous reports on S-1 monotherapy have been compared with the findings of this study (Table 3).[2,8,9,12–19] Interestingly, in two studies on efficacy of S-1 with a registration period prior to 2009, S-1 showed higher ORR in adenocarcinoma or non-SQ than in squamous cell carcinoma.[13,14] PEM was probably not administered to the analyzed populations because the efficacy of PEM was not improved in clinical trials at the time. After 2009, PEM containing treatment was mainly used for patients with non-SQ NSCLC. In 2016, a randomized phase III trial comparing S-1 with docetaxel (DTX) in patients with non-SQ NSCLC patients previously treated with platinum-based chemotherapy was reported. Subset analysis of this study suggested that PFS of S-1 was inferior to PFS of DTX in adenocarcinoma.[2] In this population, many non-SQ NSCLC (mainly adenocarcinoma) patients received PEM treatment and the registration period of this study was between July 2010 and June 2014. These studies reinforce the view that previous PEM treatment weakens the antitumor effect of S-1 and supports the presence of cross-resistance between PEM and S-1.

No ICIs were administered between PEM and S-1 in this study. Grigg et al. reported that some chemotherapies might act via immune-mediated mechanisms and chemotherapy response rates might be higher when administered after ICIs.[20] On the other hand, Kato et al. and Tamura et al. reported that subsequent S-1 after ICI did not have a better overall response rate than S-1 without ICIs in their retrospective analyses. It is still unknown whether ICIs improve the treatment efficacy of S-1.[18,19]

Exploratory analysis on the predictive factor of S-1 after PEM suggested a longer period between last PEM administration and first S-1 administration. It might therefore be an option to avoid S-1 treatment immediately after PEM.

There are several limitations in this study. First, this study was single arm study and had control arm to compare. This might have affected the results. For example, there was worse PS and patients who smoked in our study compared with the historical control, and patient characteristics in this study were slightly different from the historical control (e.g., 11.3% nonadeno-nonsquamous NSCLC cases). This might have affected the efficacy of S-1. Second, the sample size in this study was small and our study findings might have been arrived at by chance. Third, there was no diagnostic radiological central review in this study. Fourth, a more modified regimen was used in this study than in the historical control (41.5% vs. 9.3%).[9] The difference in the treatment schedule may also have affected the efficacy.

In conclusion, the efficacy of S-1 after PEM in patients with NSCLC in our study showed low ORR compared with the historical control. An option in the future might be to avoid S-1 treatment in PEM-treated patients who need tumor shrinkage. Further large-scale studies to confirm the findings in this population are essential.

CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest.

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