ORIGINAL ARTICLE

Differences in the efficacy of S-1 monotherapy according to histological type in pretreated patients with advanced non-small cell lung cancer

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Keywords

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Abstract

Background: S-1 is a novel antimetabolic agent that inhibits thymidylate synthase. The expression of thymidylate synthase is higher in squamous (Sq) non-small cell lung cancer (NSCLC) than in non-Sq NSCLC. The aim of this retrospective study was to assess the efficacy of S-1 monotherapy for advanced NSCLC according to the histological subtype.

Methods: We reviewed the clinical records of patients with advanced NSCLC treated with S-1 monotherapy as second- or third-line therapy between May 2005 and July 2012 at the Shizuoka Cancer Center.

Results: A total of 71 patients were included in this retrospective study. Patient characteristics were similar in the Sq NSCLC ($n = 15$) and non-Sq NSCLC ($n = 56$) groups, except with regard to gender and smoking status. The overall response rates were 0% (95% confidence interval [CI] 0–17%) for Sq NSCLC and 11% (95% CI 3–19%) for non-Sq NSCLC ($P = 0.33$). For Sq NSCLC and non-Sq NSCLC, the median progression-free survival times were 2.1 and 2.8 months ($P = 0.02$), respectively, and the median overall survival times were 6.1 and 10.1 months ($P = 0.01$), respectively.

Conclusion: S-1 monotherapy may be more effective in patients with non-Sq NSCLC than in those with Sq NSCLC.

Introduction

Lung cancer is the most common type of cancer, both in Japan and worldwide.^{1,2} Non-small cell lung cancer (NSCLC) accounts for 80–85% of lung cancer cases. About 50% of patients present with advanced disease at the time of diagnosis and their five-year rate of survival is less than 5%.³ Chemotherapy treatment is the standard of care for these patients, and the histology of the tumor plays a key role in the selection of the chemotherapy regimen. For example, the efficacy of pemetrexed is different for squamous (Sq) and non-Sq NSCLC, and bevacizumab

should be used in cases of non-Sq NSCLC because of its toxicity.^{4,5}

S-1, a novel antimetabolic oral agent, is a prodrug that consists of a combination 5-fluorouracil (5-FU) and tegafur (FT) and demonstrates antitumor activity against various types of tumors, for example, gastric and pancreatic cancer.^{6,7} Among chemonaïve NSCLC patients, S-1 therapy with platinum compounds demonstrated favorable overall survival (OS) in two phase III clinical trials.^{8,9} In patients with advanced NSCLC who had received previous treatment, prospective studies suggest that S-1 monotherapy is an option for further treatment.^{10,11}

Five-FU is activated into phosphorylated metabolites, such as 5-fluoro-2-deoxyuridine-5'-Monophosphate, and shows antitumor activity through the inhibition of thymidylate synthase (TS).

Ceppi *et al.* indicated that the expression of TS was higher in Sq NSCLC than in non-Sq NSCLC;¹² therefore, this study investigated whether the antitumor activity of S-1 correlated with a difference in tumor histology.

Patients and methods

Patient selection

This retrospective study included patients with advanced or relapsed NSCLC who received S-1 monotherapy following the failure of previous systemic chemotherapy at the Shizuoka Cancer Center between May 2005 and July 2012. Eligibility criteria for this study included S-1 administration as second- or third-line chemotherapy (treatment with epidermal growth factor receptor-tyrosine kinase inhibitors [EGFR-TKI] was not counted as a previous treatment regimen), an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), and adequate baseline organ function.

Patients were divided into two groups, Sq or non-Sq NSCLC. Pathological diagnosis was based upon the World Health Organization classification for cell types using immunohistochemical analysis for the markers thyroid transcription factor 1, CAM 5.2, and p63.

Treatment schedule

S-1 was orally administered twice a day following meals. The dose of S-1 administered was determined according to the patient's body surface area (BSA) as follows: 80 mg/day for $BSA < 1.25 \text{ m}^2$, 100 mg/day for $1.25 \text{ m}^2 \leq BSA < 1.50 \text{ m}^2$, or 120 mg/day for $BSA \geq 1.50 \text{ m}^2$. Two treatment schedules were adopted in our hospital, a four week administration followed by two weeks of rest repeated every six weeks, and a two week administration followed by one week of rest repeated every three weeks. Administration of S-1 was continued until disease progression or the development of intolerable toxicities.

Evaluation and statistical analysis

The antitumor response was assessed every six to eight weeks according to RECIST. Adverse events were evaluated in accordance with the common terminology criteria for adverse events (CTCAE) version 4.0. Progression-free survival (PFS) was calculated as the time from the first administration of S-1 monotherapy to the date of disease progression, and OS was

calculated as the time from the first administration of S-1 monotherapy to the date of mortality from any cause. The OS rate was censored at the date of the last visit for those patients whose deaths could not be confirmed. Patients' characteristics and overall response rates (ORRs) were compared using Fisher's exact test. PFS and OS were estimated using the Kaplan–Meier method and compared using the log-rank test. Statistical analysis was performed using JMP version 8.0 (SAS Institute Inc., Cary, NC, USA). Probability (*P*) values of <0.05 were considered to be statistically significant.

Results

A total of 71 patients, 15 with Sq NSCLC and 56 with non-Sq NSCLC, were included in this study. The clinical characteristics of the patients are shown in Table 1. The median patient age was 67 years (range 32–82), 49 (69%) were male, 56 (79%) were previous or current heavy smokers, 58 (82%) had an ECOG PS of 0–1, and 53 (75%) had stage IV disease. Thirty-nine patients (55%) were being treated with S-1 monotherapy as third-line therapy. The patient backgrounds did not differ significantly between the Sq and non-Sq groups, except in terms of gender and smoking status. Chemotherapy regimens as first line treatment are shown in Table 2 (EGFR-TKI was not counted as a previous treatment regimen). In both Sq and non-Sq NSCLC groups, 13 (87%) and 47 (84%) patients received platinum-based chemotherapy ($P = 0.79$), respectively.

In the Sq group, 12 patients (80%) received the standard S-1 regimen (four weeks administration followed by two

Table 1 Patient characteristics

	Sq (<i>n</i> = 15)	Non-Sq (<i>n</i> = 56)	<i>P</i> -value
Age (years)			0.91
Median	67	68	
Range	53–76	32–82	
Gender (no.)			0.03
Male	14	35	
Female	1	21	
Smoking status (no.)			0.03
Non/light smoker	0	15	
Previous/current	15	41	
ECOG performance status (no.)			0.85
0/1	12	46	
2	3	10	
Clinical stage (no.)			0.11
IIIB	5	7	
IV	8	45	
Postoperative relapse	2	4	
Treatment line (no.)			0.14
2	4	28	
3	11	28	

ECOG, Eastern Cooperative Oncology Group; Non-Sq, non-squamous; Sq, squamous.

Table 2 Chemotherapy regimens as first line treatment

	Sq (n = 15)	Non-Sq (n = 56)	P-value
Platinum-based chemotherapy	13	47	0.79
CDDP+GEM	1	7	
CDDP+DTX	1	2	
CDDP+PEM	0	13	
CDDP+PEM+Axitinib	0	3	
CDDP+CPT-11	0	1	
CBDCA+PTX	7	14	
CBDCA+PTX+Bev	0	1	
CBDCA+GEM	3	4	
CBDCA+PEM	0	2	
CDGP+DTX	1	0	
Monotherapy	2	9	
VNR	1	3	
GEM	1	1	
DTX	0	4	
PEM	0	1	

Bev, Bevacizumab; CBDCA, Carboplatin; CDDP, Cisplatin; CDGP, Nedaplatin; CPT-11, Irinotecan; DTX, Docetaxel; GEM, Gemcitabine; Non-Sq, non-squamous; PEM, Pemetrexed; PTX, Paclitaxel; Sq, squamous; VNR, Vinorelbine.

weeks of rest, every six weeks), and three patients (20%) received the modified S-1 regimen (two weeks administration followed by one week of rest, every three weeks) for the first S-1 cycle. In the non-Sq group, 38 patients (75%) received the standard S-1 regimen, and 13 patients (25%) received the modified S-1 regimen for the first S-1 cycle. Treatment schedules did not differ significantly between the two groups ($P = 0.79$). Schedule modification or dose reduction as a result of treatment-related toxicities or patient refusal was observed in three patients (20%) in the Sq group and 11 patients (34%) in the non-Sq group ($P = 0.41$). At the time of the last data collection, S-1 therapy had been withdrawn in all patients. The most common reason for early withdrawal was disease progression (69 patients).

In the 71 patients, the ORR was 8% (95% confidence interval [CI]: 2–17%), the median PFS time was 2.7 months (95% CI: 2.0–2.8 months), and the median OS time was 9.0 months (95% CI: 7.5–12.2 months). For the Sq and non-Sq NSCLC groups, the ORRs were 0% (95% CI: 0–17%) and 11% (95% CI: 3–19%), respectively ($P = 0.33$). Figure 1 shows a waterfall plot of the best response according to the histological type. In the non-Sq NSCLC group, 19 of the 56 patients (34%) demonstrated some kind of response, and six patients (11%) experienced a partial response (PR). In the Sq NSCLC group, one patient (7%) demonstrated minor tumor shrinkage and none experienced PR. In both the Sq and non-Sq NSCLC groups, the median PFS times were 2.1 and 2.8 months (hazard ratio [HR] = 2.1, 95% CI: 1.1–3.6, $P = 0.02$) (Fig. 2), respectively, and the median OS times were 6.1 and 10.1 months (HR = 2.3, 95% CI: 1.2–4.1, $P = 0.02$) (Fig. 3), respectively.

Figure 1 A waterfall plot of the best response compared with baseline according to histological type (squamous [Sq], white bars; non-Sq, black bars). In the non-Sq non-small cell lung cancer (NSCLC) group, 19 of the 56 patients (34%) demonstrated a response, and six patients (11%) experienced a partial response. In the Sq NSCLC group, only one patient (7%) demonstrated minor tumor shrinkage, and none experienced a partial response.

Twelve patients experienced serious adverse events (AEs). The grade 3 hematologic toxicities were anemia (five patients), leukopenia, and neutropenia. The grade 3 non-hematologic toxicities were hyponatremia (two patients); watering eyes (two patients); and anorexia, oral mucositis, fatigue, pneumonia, and diarrhea (each experienced by one patient). No grade 4 AEs or treatment-related deaths were observed. Seven patients on the standard S-1 regimen and five patients on the modified S-1 regimen experienced grade 3 toxicities. Grade 3 toxicities were not associated with treatment schedules ($P = 0.12$).

Figure 2 Kaplan-Meier curves for progression-free survival (PFS) according to histological type (squamous [Sq], bold line; non-Sq, dotted line). The median PFS times were 2.1 and 2.8 months for the Sq and non-Sq NSCLC groups, respectively (hazard ratio [HR] = 2.1, 95% confidence interval [CI]: 1.1–3.6, $P = 0.02$).

Figure 3 Kaplan-Meier curves for overall survival (OS) according to histological type (squamous [Sq], bold line; non-Sq, dotted line). The median OS times were 6.1 and 10.1 months for the Sq and non-Sq NSCLC groups, respectively (hazard ratio [HR] = 2.3, 95% confidence interval [CI]: 1.2 to 4.1, $P = 0.02$).

Overall, 30 patients (55%) with non-Sq NSCLC and seven patients (47%) with Sq NSCLC received post-treatment ($P = 0.63$).

Discussion

In the present study, the efficacy of S-1 monotherapy was retrospectively analyzed in 71 patients with advanced or relapsed NSCLC. S-1 demonstrated more favorable efficacy in patients with non-Sq NSCLC than in those with Sq cell lung cancer. There was no significant difference in the ORRs between the two groups, although the non-Sq cell group demonstrated a better ORR than the Sq group (11% vs. 0%, Fig. 1). The median PFS and OS times were significantly longer in the non-Sq group (Figs 2, 3).

In prior studies in which patients had received previous treatment for NSCLC, S-1 monotherapy provided promising results, with an ORR of six to 20% and a median PFS time of 1.4–4.2 months;^{10,11} however, the accrued number of patients in these studies was relatively small (approximately 50 patients). Our study included a large number of patients, and our efficacy results were consistent with these prior studies. The correlation between histological differences in NSCLC and the efficacy of S-1 is a matter of debate. Yamamoto *et al.* reported, in a combined analysis of two phase II clinical trials of S-1 plus cisplatin in patients with chemo-naïve NSCLC,¹² that the efficacy results for Sq and non-Sq NSCLC were not different. Ichinose *et al.* conducted a phase II clinical trial of S-1 monotherapy for untreated NSCLC patients.¹³ Although the ORR was higher for adenocarcinoma than for Sq cell lung cancer (26% vs. 10%), PFS and OS data were not determined in this trial. We hypothesized that the expression level of TS

may account for these efficacy differences. TS, a pharmacological target of S-1, is highly expressed in Sq NSCLC compared to non-Sq NSCLC.¹⁴

A relatively new antifolate drug, pemetrexed, inhibits the growth of a variety of tumor types. With regard to pemetrexed, Takezawa *et al.* reported a high level of TS expression confers a reduced sensitivity to pemetrexed.¹⁵ As well as pemetrexed, a low TS expression level may have a survival advantage in treatment with S-1 monotherapy in patients with non-Sq NSCLC more than Sq. With this in mind, we divided patients into two groups, Sq and non-Sq NSCLC. None of the patients in the Sq group demonstrated a PR, whereas 11% of the patients in the non-Sq group demonstrated a PR. The median PFS and OS times were significantly longer in the non-Sq group than in the Sq group.

Two limitations of this study must be addressed. First, as a result of the low number of available specimens, we could not investigate the direct relationship between the TS expression level and the efficacy of S-1. However, we believe this study should have some impact on clinical practice, because there are few previous reports addressing the effect of Sq cell histology on the efficacy of S-1. Second, because this was a retrospective study, the timing of the evaluation was dependent upon the individual investigators.

Conclusion

In conclusion, S-1 monotherapy, in pretreated NSCLC may be more effective in patients with non-Sq NSCLC than in those with Sq NSCLC. A phase III clinical trial to determine the efficacy of S-1 with docetaxel in NSCLC patients is currently ongoing in east Asia. Analysis of efficacy according to histological subtype may help determine the optimal treatment strategy using S-1.

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