A Retrospective Study of the Novel Combination of Paclitaxel and S1 for Pretreated Advanced Non-Small Cell Lung Cancer

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Key Words

Non-small cell lung cancer • Chemotherapy • Paclitaxel • S1 • Multivariate analysis • Shared frailty Cox model

Abstract

Background: Recently, multiple-line chemotherapy has become popular for non-small cell lung cancer (NSCLC). The survival time of patients is influenced by patient characteristics and subsequent treatments. **Methods:** The usefulness of paclitaxel plus S1 (PTX+S1) was evaluated in 46 pretreated NSCLC patients. Time from the start of individual regimens till the start of the next one (TNR) was calculated for regimens administered to the study population including PTX+S1 and analyzed by the shared frailty Cox model. **Results:** The response rate and the median progression-free survival time of PTX+S1 were 32.6% and 253 days, respectively. Substantial difference in TNR was observed in epidermal growth factor receptor mutation status and in line and type of regimens, but not in stage, age, sex, performance status and histology, by univariate analysis. Multivariate analysis revealed that PTX+S1 was only one factor to prolong TNR. **Conclusion:** Because of long progression-free survival and long TNR, further evaluation of PTX+S1 is necessary.

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. Approximately 85% of lung cancer patients have non-small cell lung cancer (NSCLC). Most NSCLC patients have advanced disease at presentation, and a combination of platinum with third-generation anticancer agents is now considered as standard first-line chemotherapy for advanced NSCLC patients [1, 2]. However, most NSCLC patients are either refractory to first-line chemotherapy or show relapse after an initial response, indicating the importance of treatment with second- and later-line drugs.

S1 (Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) is an oral fluoropyrimidine formulation which combines tegafur, 5-chloro-2,4-dihydroxy-pyridine and potassium oxonate in the molar ratio of 1:0.4:1 [3]. Tegafur is a prodrug of 5-fluorouracil (5-FU), and approximately 90% of 5-FU is metabolized by the liver enzyme dihydropyrimidine dehydrogenase [4, 5]. 5-Chloro-2,4-dihydroxy-pyridine increases the plasma concentration of 5-FU by inhibiting dihydropyrimidine dehydrogenase, whereas it attenuates the cardiotoxicity and neurotoxicity of 5-FU by reducing the production of fluoro- β -alanine [6, 7]. Oxonate is distributed selectively to the small and the large intestines; here, it inhibits the phosphorylation of 5-FU by suppress-

ing orotate/pyrimidine phosphoribosyltransferase, thereby reducing the incidence of gastrointestinal toxicity of 5-FU [8]. Thus, S1 is designed to enhance antitumor activity and reduce the gastrointestinal toxicity of 5-FU. Recently, S1 has been used to treat several types of cancer, in addition to gastric cancer [9–11]. In a phase II trial involving 59 advanced NSCLC patients, a 4-week duration of S1 therapy every 6 weeks showed a response rate of 22.0% and a median survival time (MST) of 10.2 months [12]. The combined use of paclitaxel and S1 (PTX+S1) showed additive synergistic antitumor effects [13]. This combination was shown to be safe and effective, with a response rate of 45% and an MST of 8.5 months in a phase II study involving 39 patients with advanced gastric cancer [14]; however, there is almost no evidence of the efficacy of this combination in NSCLC. Therefore, we studied the treatment of advanced NSCLC with PTX+S1 and retrospectively analyzed the results. Triweekly regimens are common in chemotherapy for NSCLC, but biweekly regimens have also been studied [15].

Although parameters such as progression-free survival (PFS) and overall survival (OS) are important endpoints in clinical trials for lung cancer, they are known to be influenced by treatments administered after progression and/or patient selection. The purpose of this study was to evaluate the efficacy of PTX+S1 in itself and in comparison with other regimens administered to the study population.

Patients and Methods

From September 2007 to April 2010, 46 pretreated advanced NSCLC patients received PTX+S1. S1 was administered twice a day, orally, from day 1 to day 14, followed by a 2-week off period. PTX was administered intravenously on day 1 and day 15. Cycles were repeated every 4 weeks. Eligibility criteria of this study included cytologically or histologically diagnosed NSCLC, inoperable and not amenable to curative radiation, second- or later-line treatment, an Eastern Cooperative Oncology Group performance status (PS) of 0–1, as well as consent for treatment with PTX+S1. The use of PTX or S1, but not PTX+S1 itself, in preceding treatments was accepted.

On the basis of the trial of PTX+S1 for advanced gastric cancer, we adopted the doses of PTX and S1 to be 120 and 80 mg/m², respectively. The dose of PTX ranged from 70 to 120 mg/m², depending on patient conditions, and the dose of S1 was 80 mg/m²/day, except when dose reduction was required. When myelosuppression was prolonged, PTX on day 15 was skipped in the subsequent cycles. Treatment was continued until disease progression, appearance of unacceptable toxicity, withdrawal of consent by the patient, or termination of treatment by the attending physician.

Tumor response was evaluated using the Response Evaluation Criteria for Solid Tumors, version 1.0. Because this was a retro-

spective analysis, tumor response could not be confirmed. Toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 3.0. The median follow-up period was 639 days. The mean $\pm$ SD interval time of tumor assessment by using chest and abdominal computed tomography or positron emission tomography/computed tomography was 60.5 $\pm$ 34.3 days. In addition, almost all patients visited our hospital once or twice a month during the treatment, and chest radiography and blood examination were performed during their visit.

One way to test the efficacy of a regimen is to compare the PFS of the regimen with that of historical controls. However, it is well known that PFS is influenced by patient selection. Patients with a good prognosis may show a long PFS for a regimen, which is independent of the efficacy of a therapy. Therefore, comparison with historical data sometimes leads to wrong conclusions. To avoid this, we defined the duration of a regimen as the period between the start of that regimen and the start of the next regimen (time to next regimen, TNR) and tried to approximate PFS with TNR. This method is expected to make it possible to evaluate the efficacy of a regimen in comparison with other regimens used in the same patient population.

Statistical Analysis

Statistical analysis was done using SPSS Statistics version 17.0 and Stata version 11.2. To detect the factors contributing to a long TNR, the effect of gender, Eastern Cooperative Oncology Group PS (0 vs. 1/2), stage (III vs. IV), histology (adenocarcinoma vs. non-adenocarcinoma), line of treatment (first, second, third vs. $\geq$ fourth) and chemotherapy regimens were analyzed using Kaplan-Meier analysis. We categorized the treatment regimens as follows: platinum doublets, non-platinum doublets, PTX+S1, pemetrexed or docetaxel (L+D), epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), single cytotoxic drugs mainly of third generation, and other than pemetrexed and docetaxel. First-line chemotherapy with curative thoracic radiation was excluded from the analysis because it contained radiation. When combined with cytotoxic drugs, bevacizumab (6 regimens) and EGFR-TKI (4 regimens) were neglected. Exon 19 deletion and L858R mutation in the exon 21 of EGFR were classified as active mutations; other EGFR mutations and wild-type EGFR were classified as non-active EGFR. TNR was also analyzed using the Cox proportional hazard model with shared frailty to consider the intra-patient correlation of TNR and by setting each patient's identification as a random effect [16]. PFS and TNR in PTX+S1 were compared in 29 patients, for whom the data of both PFS and TNR were available.

Results

Patient Characteristics

Characteristics of 46 patients are presented in table 1. Most were men, and almost all patients had a PS of 0–1. Histologically, 35 patients (76.1%) had adenocarcinoma. There were 1 (2.2%), 9 (19.6%) and 36 (78.3%) patients with stage IIIA, IIIB and IV, respectively. PTX+S1 was performed as second- (n = 12), third- (n = 11) and

Table 1. Patient characteristics

Characteristics		n
Patients	Total	46
Sex	Female	11 (23.9)
	Male	35 (76.1)
Age	Median	62 [40–75]
ECOG PS	0	5 (10.9)
	1	40 (87.0)
	2	1 (2.2)
Histology	Ad	35 (76.1)
	Sq	10 (21.7)
	AdSq	1 (2.2)
Stage	IIIA	1 (2.2)
	IIIB	9 (19.6)
	IV	36 (78.3)
Number of organs with distant metastasis	0	6 (13.0)
	1	19 (41.3)
	2	15 (32.6)
	3	5 (10.9)
	4	1 (2.2)
EGFR mutation status ¹	None	34 (73.9)
	Active EGFR	12 (26.1)
Number of prior regimens	1	12 (26.1)
	2	11 (23.9)
	3	11 (23.9)
	>4	12 (26.1)
Prior treatment with PTX or S1	None	33 (71.7)
	PTX	7 (15.2)
	S1	4 (8.7)
	Both	2 (4.3)

Figures in parentheses are percentages; figures in brackets indicate the range. ECOG = Eastern Cooperative Oncology Group; Ad = adenocarcinoma; Sq = squamous cell carcinoma; AdSq = adenosquamous carcinoma.

¹ Active EGFR includes deletion in exon 19 and L858R mutation, and one L861Q mutation and wild-type EGFR were included in none.

≥fourth-line (n = 23) chemotherapy. Thirty-eight patients (82.6%) had measurable lesions. EGFR-active mutations were detected in 12 patients (26.1%). The median number of cycles of PTX+S1 was 6 (range 1–26). Three patients were on PTX+S1 treatment at data cut-off time. Seven, 4 and 2 patients had a history of treatment with chemotherapy containing PTX, S1 and both, respectively, before treatment with PTX+S1.

Toxicity and Efficacy

Toxicity data are summarized in table 2. Grade 3 or higher neutropenia was observed in 14 (30.4%) and febrile

Table 2. Hematological and non-hematological toxicities

Toxicities	Grade	
	3	4
Leukopenia	4 (8.7)	0
Neutropenia	11 (23.9)	3 (6.5)
Anemia	1 (2.2)	0
Thrombocytopenia	0	0
Nausea	0	0
Fatigue	1 (2.2)	0
Arthralgia	0	0
Rash	0	0
Sensory neuropathy	2 (4.3)	0
Alopecia	0	0
Febrile neutropenia	3 (6.5)	0
Infection	2 (4.3)	0
Pneumonitis	3 (6.5)	0
Arrhythmia	0	0
Cerebrovascular disease	0	1 (2.2)

Figures in parentheses are percentages.

neutropenia was observed in 3 (6.5%) patients. Grade 3 fatigue and grade 3 sensory neuropathy occurred in 1 (2.2%) and 2 (4.3%) patients, respectively. Three patients (6.5%) developed pneumonitis; pneumonitis was mild and appeared to be ascribed to prior treatment in 2 patients (carboplatin plus PTX with radiation and gemcitabine, respectively). Although a grade 4 cerebrovascular event occurred in 1 (2.2%) patient, it was unclear whether it had any relevance to PTX+S1. There were no treatment-related deaths.

Fifteen patients exhibited partial response and 15 stable disease. The response rate was 32.6% and the disease control rate was 65.0%. MST and median PFS were 735 and 253 days, respectively (fig. 1).

Multivariate Analysis of the Duration of the Regimens

PFS with pemetrexed and docetaxel, the recent standard regimens in second-line settings, was reported to be 3.1 and 3.0 months, respectively, in previously treated NSCLC patients [17]. In our study, PTX+S1 showed longer PFS. To extract the factors contributing to the long PFS observed, TNR of 196 regimens in 46 patients was analyzed. The representative results of the Kaplan-Meier analysis are shown in figure 2. No appreciable difference in TNR was observed in relation to age, sex, PS, histology and stage (fig. 2d), whereas small differences were observed because of EGFR mutation status (fig. 2c) and

Table 3. Multivariate analysis of TNR

Covariate	Patients	HR	p
Type of regimen			
L+D	48	1	–
NonP doublet	12	0.523 (0.255–1.073)	0.077
P doublet	54	0.775 (0.475–1.262)	0.305
PTX+S1	34	0.378 (0.235–0.606)	0
TKI	28	1.380 (0.816–2.335)	0.229
Other	20	0.910 (0.509–1.629)	0.752
EGFR status			
Wild	80	1	–
Unknown	56	1.025 (0.650–1.615)	0.917
Mutant	60	0.960 (0.556–1.657)	0.883
Stage			
III	64	1	–
IV	162	1.043 (0.623–1.748)	0.872
Line			
1st	34	1	–
2nd	41	0.946 (0.551–1.625)	0.840
3rd	33	0.992 (0.540–1.822)	0.980
≥4th	88	1.455 (0.831–2.546)	0.189

Figures in parentheses are 95% confidence intervals.

$\theta = 0.147$, significant level of the likelihood ratio test of $H_0: \theta = 0$; $p = 0.008$. HR = Hazard ratio; NonP doublet = non-platinum doublets; P doublet = platinum doublet; TKI = EGFR-TKI; Other = other regimens, mainly third-generation single cytotoxic agents other than pemetrexed and docetaxel.

line of treatment (fig. 2b). The highest difference observed was attributable to the type of regimen (fig. 2a); median TNR ranged from 87 days (EGFR-TKI) to 239 days (PTX+S1). TNR of the L+D group was 104 days. PTX+S1 showed the longest TNR among the regimens studied.

Multivariate analysis was performed using the Cox proportional hazard model with shared frailty. The Cox model with shared frailty of patients' identification showed that the estimated frailty variance was $\hat{\theta} = 0.147$, which was the level of the likelihood ratio test of $H_0: \theta = 0$ ($p = 0.008$). Therefore, TNR scores were analyzed as stratified data of individual patients. When stage, line of treatment, EGFR mutation status and type of regimen were included in the analysis, PTX+S1 was only one factor to show statistically significant prolongation of TNR (table 3). Non-platinum doublets exhibited the tendency of prolonged TNR (HR = 0.523, $p = 0.077$), and TNR and PFS were well correlated in PTX+S1 treatment (correlation coefficient = 0.963, $p < 0.0001$; data not shown).

Fig. 1. OS and PFS of the patients treated with PTX+S1. mPFS = Median PFS.

Discussion

In the phase III Lung Cancer Evaluation of TS1 trial, a 3-week cycle of carboplatin (on day 1) plus S1 (on days 1–14) was compared with carboplatin plus PTX in chemotherapy-naïve advanced NSCLC patients. Carboplatin plus S1 showed non-inferiority to carboplatin plus PTX with generally milder toxicities [18]. Non-platinum doublets containing S1 were also studied in phase II studies. Irinotecan plus S1 produced a response rate of 28.6%, a median PFS of 4.9 months and an MST of 15 months in the first-line setting [19]. In chemotherapy-naïve patients, S1 in combination with gemcitabine showed a response rate of 23.1–30.6%, with an MST of 15.5–18.8 months [20]. When combined with docetaxel, a response rate of 18.4%, a median PFS of 4.4 months and an MST of 16.1 months were reported for previously treated NSCLC patients [21]. These results are comparable to those of standard platinum-based regimens.

In our study, PTX+S1 produced a high response rate with a good toxicity profile. Since PFS observed in standard second-line treatments for NSCLC ranges between 2.0 and 7.5 months, PFS of 253 days by PTX+S1 is impressive. However, there is a possibility that these results are attributable to selection bias. Actually, OS in this study was 1,308 days when calculated from the start of the first-line treatment, suggesting that patients with a good prognosis were recruited for the study. This is possible because there was no restriction to the number of preceding lines of treatment before PTX+S1, which may have led to an

Fig. 2. Kaplan-Meier analysis of TNR. Numbers in parentheses indicate median TNR in days. **a** L+D (106), platinum doublets (P double, 157), non-platinum doublets (NonP doublets, 182), PTX+S1 (239), EGFR-TKI (TKI, 87). **b** First line (152), 2nd line

(160), 3rd line (133), 4th line (115). **c** Wild-type EGFR (N, 120), EGFR mutation not tested (NM, 131), active EGFR mutation (P, 140). **d** Stage III (140), stage IV (127).

increase in the chance of accrual of patients who had received multiple lines of chemotherapy and therefore were endowed as long survivors.

To evaluate the contribution of PTX+S1 per se to long PFS, we analyzed TNR of whole regimens that were used for the patients in this study. As a result, PTX+S1 appeared to be the only factor that produced statistically

significant prolongation of TNR in univariate and multivariate analyses. The median TNR of L+D was 104 days, indicating that our patients showed a standard response to pemetrexed or docetaxel. Long PFS by PTX+S1 appears to be derived, at least partly, from the effect of PTX+S1 itself. It may look strange that the ratio of TNR of platinum doublets, the strongest regimen, was 0.775. This may

be explained by the fact that platinum doublets are not administered over 4–6 cycles, which may give some idea in understanding recent developments in maintenance therapy.

Our study has several limitations. First, TNR was not established sufficiently. However, PFS and TNR are well correlated, at least in PTX+S1 treatment in this study, indicating that TNR may become a surrogate of PFS. New lines usually start at disease progression in the treatment of NSCLC. Therefore, it is reasonable to postulate that TNR approximates PFS. TNR can be determined for almost all regimens administered to a study population. Long TNR may be attributable to treatment toxicities, but it is not so frequent in the treatment of advanced NSCLC. Second, long survivors may have been recruited for the study, as mentioned above. We cannot exclude the possibility that PTX+S1 is able to produce long PFS only in long survivors. Third, this study included lung cancer patients who harbored activated EGFR mutations. Recent data clearly show the distinct activity of EGFR-TKI in patients with tumors with activated EGFR mutations. In our study, 12 patients (26.1%) had tumors with activated

EGFR mutations, but only 3 of them underwent treatment with EGFR-TKI after PTX+S1 treatment, and 1 of them had squamous cell carcinoma. Therefore, the effect of EGFR-TKI on OS by PTX+S1 will be limited.

Long TNR may be able to contribute to prolongation of OS. In recent NSCLC clinical trials, sometimes prolongation of PFS was observed without its translation to OS. This discrepancy is partly explained by the effect of post-trial treatments. Actually, multiple lines of chemotherapy are performed in recent treatments of NSCLC. In this situation, it may be critical to evaluate not only the regimen of interest but also the total regimens administered. However, unfortunately, it is difficult to analyze the PFS effect of post-trial treatments on OS, because PFS is not generally assessed so rigorously outside a trial setting. TNR analysis may partly address this shortcoming.

In conclusion, because PTX+S1 was effective and showed long treatment duration in our study population, further evaluation of this combination is necessary. The analysis of duration of treatments may be useful to evaluate chemotherapy regimens.

References

- Ohe Y, Ohashi Y, Kubota K, Tamura T, Nakagawa K, Negoro S, Nishiwaki Y, Saijo N, Ariyoshi Y, Fukuoka M: Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007;18:317–323.
- Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH, Eastern Cooperative Oncology Group: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
- Shirasaka T, Nakano K, Takechi T, Satake H, Uchida J, Fujioka A, Saito H, Okabe H, Oyama K, Takeda S, Unemi N, Fukushima M: Antitumor activity of 1 M tegafur-0.4 M 5-chloro-2,4-dihydropyridine-1 M potassium oxonate (S1) against human colon carcinoma orthotopically implanted into nude rats. *Cancer Res* 1996;56:2602–2606.
- Fujii S, Shimamoto Y, Ohshimo H, Imaoka T, Motoyama M, Fukushima M, Shirasaka T: Effects of the plasma concentration of 5-fluorouracil and the duration of continuous venous infusion of 5-fluorouracil with an inhibitor of 5-fluorouracil degradation on Yoshida sarcomas in rats. *Jpn J Cancer Res* 1989;80:167–172.
- Heggie GD, Sommadossi JP, Cross DS, Huster WJ, Diasio RB: Clinical pharmacokinetics of 5-fluorouracil and its metabolites in plasma, urine, and bile. *Cancer Res* 1987;47:2203–2206.
- Robben NC, Pippas AW, Moore JO: The syndrome of 5-fluorouracil cardiotoxicity. An elusive cardiopathy. *Cancer* 1993;71:493–509.
- Kato T, Shimamoto Y, Uchida J, Ohshimo H, Abe M, Shirasaka T, Fukushima M: Possible regulation of 5-fluorouracil-induced neuro- and oral toxicities by two biochemical modulators consisting of S1, a new oral formulation of 5-fluorouracil. *Anticancer Res* 2001;21:1705–1712.
- Shirasaka T, Shimamoto Y, Fukushima M: Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res* 1993;53:4004–4009.
- Oh SY, Lee G-W, Kim HG, Kim TH, Kim HJ, Kang JH: Phase II trial of S-1 in combination with oxaliplatin in previously untreated patients with recurrent or inoperable biliary tract cancer. *Chemotherapy* 2008;54:479–484.
- Hasegawa H, Fujitani K, Kurokawa Y, Hirao M, Nakazuru S, Mita E, Tsujinaka T: Effect of S-1 adjuvant chemotherapy on survival following recurrence and efficacy of first-line treatment in recurrent gastric cancer. *Chemotherapy* 2010;56:436–443.
- Kogashiwa Y, Yamauchi K, Nagafuji H, Matsuda T, Tsubosaka T, Karaho T, Maruyama T, Kohno N: Phase I study of S-1 plus nedaplatin in patients with advanced/recurrent head and neck cancer. *Chemotherapy* 2008;54:479–484.
- Kawahara M, Furuse K, Segawa Y, Kawahara M, Furuse K, Segawa Y, Yoshimori K, Matsui K, Kudoh S, Hasegawa K, Niitani H, S-1 Cooperative Study Group (Lung Cancer Working Group): Phase II study of S1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. *Br J Cancer* 2001;85:939–943.
- Sakurai Y, Yoshida I, Kamoshida S, Inaba K, Isogaki J, Komori Y, Uyama I, Tsutsumi Y: Effects of combined administration of DPD-inhibitory oral fluoropyrimidine, S1, plus paclitaxel on gene expressions of fluoropyrimidine metabolism-related enzymes in human gastric xenografts. *Ann Surg Oncol* 2008;15:2301–2309.
- Nakajo A, Hokita S, Ishigami S, Miyazono F, Etoh T, Hamanoue M, Maenohara S, Iwashita T, Komatsu H, Satoh K, Aridome K, Morita S, Natsugoe S, Takiuchi H, Nakano S, Maehara Y, Sakamoto J, Aikou T, Kyushu Taxol TS-1 Study Group: A multicenter phase II study of biweekly paclitaxel and S1 combination chemotherapy for unresectable or recurrent gastric cancer. *Cancer Chemother Pharmacol* 2008;62:1103–1109.

- 15 Chelis L, Xenidis N, Amrantidis K, Prassopoulos P, Chamalidou E, Neanidis K, Mikroulis D, Chatzaki E, Karakitsos P, Kakolyris S: Biweekly vinorelbine and gemcitabine as second-line treatment and beyond in non-small cell lung cancer. *Chemotherapy* 2010; 56:353–358.
- 16 Therneau TM, Grambsch PM: *Modeling Survival Data: Extending the Cox Model*. New York, Springer, 2000.
- 17 Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, Gatzemeier U, Tsao TC, Pless M, Muller T, Lim HL, Desch C, Szondy K, Gervais R, Shaharyar, Manegold C, Paul S, Paoletti P, Einhorn L, Bunn PA Jr: Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589–1597.
- 18 Okamoto I, Yoshioka H, Morita S, Ando M, Takeda K, Seto T, Yamamoto N, Saka H, Asami K, Hirashima T, Kudoh S, Satouchi M, Ikeda N, Iwamoto Y, Sawa T, Miyazaki M, Tamura K, Kurata T, Fukuoka M, Nakagawa K: Phase III trial comparing oral S-1 plus carboplatin with paclitaxel plus carboplatin in chemotherapy-naïve patients with advanced non-small-cell lung cancer: results of a West Japan Oncology Group study. *J Clin Oncol* 2010;28:5240–5246.
- 19 Okamoto I, Nishimura T, Miyazaki M, Yoshioka H, Kubo A, Takeda K, Ebi N, Sugawara S, Katakami N, Fukuoka M, Nakagawa K: Phase II study of combination therapy with S1 and irinotecan for advanced non-small cell lung cancer: West Japan Thoracic Oncology Group 3505. *Clin Cancer Res* 2008;14:5250–5254.
- 20 Satouchi M, Kotani Y, Katakami N, Shimada T, Urata Y, Yoshimura S, Funada Y, Hata A, Ando M, Negoro S: Randomized phase II study of two different schedules of gemcitabine and oral TS1 in chemo-naïve patients with advanced non-small cell lung cancer. *J Thorac Oncol* 2010;5:696–701.
- 21 Yanagihara K, Yoshimura K, Niimi M, Yasuda H, Sasaki T, Nishimura T, Ishiguro H, Matsumoto S, Kitano T, Kanai M, Misawa A, Tada H, Teramukai S, Mio T, Fukushima M: Phase II study of S1 and docetaxel for previously treated patients with locally advanced or metastatic non-small cell lung cancer. *Cancer Chemother Pharmacol* 2010;66:913–918.