Pooled Analysis of S-1 Trials in Non-Small Cell Lung Cancer According to Histological Type

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Abstract. *Background: The antimetabolic agent S-1 inhibits thymidylate synthase similar to pemetrexed, but through a different mechanism of action. Whether the antitumour activity of S-1 depends on histological type remains unclear. We analysed pooled data from 2 phase II clinical studies of cisplatin and S-1 in patients with previously untreated advanced non-small cell lung cancer. Patients and Methods: We comprised 110 patients with stage IIIB or IV non–small cell lung cancer. Univariate and multivariate analyses were performed to determine the effects of histological type on progression-free survival and response rates. Results: On pooled analysis of the data, according to histological type, median progression-free survival was 3.8 months in patients with squamous cell carcinoma and 4.4 months in those with non-squamous cell carcinoma. Both analyses showed that progression-free survival and response rate did not differ significantly. Conclusion: Unlike molecular targeted agents and pemetrexed, a combination of cisplatin and S-1 may be no difference in response according to histological type.*

Lung cancer continues to affect more than 100 million people worldwide. About 80% of all cases are non-small cell lung cancer (1). Stage IV advanced lung cancer is usually treated by chemotherapy with anticancer drugs; however, outcomes remain far from satisfactory. Various treatment regimens have been developed to improve survival.

The anticancer drug pemetrexed, classified as an antimetabolic agent, has recently become standard treatment for malignant pleural mesothelioma. Pemetrexed acts by inhibiting the activity of several enzymes, including thymidylate synthase (TS), which is involved in the *de novo* synthesis of thymidine triphosphate, dihydrofolate reductase, which reduces folic acid to its active form required for DNA synthesis, and glycinamide ribonucleotide formyl transferase, which participates in purine synthesis (2). A randomised clinical trial comparing pemetrexed with docetaxel as second-line treatment in patients with non-small cell lung cancer was conducted outside of Japan (3). The trial failed to establish that pemetrexed was superior to docetaxel in terms of efficacy, but it had lower toxicity. Pemetrexed was therefore approved by the Food and Drug Administration and is now used as a standard treatment in the United States. Subsequently, a retrospective analysis was performed to examine the effectiveness of pemetrexed according to histological type (squamous cell carcinoma *vs*. non-squamous cell carcinoma). Pemetrexed was found to improve survival in patients with non-squamous cell carcinoma, but was less effective than docetaxel for squamous cell carcinoma (4). Scagliotti *et al*. demonstrated that cisplatin plus pemetrexed is not inferior to cisplatin plus gemcitabine in terms of overall survival in patients with advanced non-small cell lung cancer who received first-line chemotherapy (5). That study included an analysis of response according to histological type.

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Cisplatin plus pemetrexed was shown to be associated with significantly better survival in patients with non-squamous cell carcinoma, although this was not a primary endpoint of the investigation. On the basis of these results, cisplatin plus pemetrexed was approved for the first-line treatment of non-small cell lung cancer in the United States and Europe; however, squamous cell carcinoma was excluded from the approved indication. A phase III study assessing the benefits of maintenance therapy with pemetrexed after platinum-doublet chemotherapy showed that pemetrexed significantly improves progression-free survival and overall survival as compared with placebo in patients with non-squamous cell carcinoma. In squamous cell carcinoma, however, pemetrexed was associated with slightly shorter progression-free survival and overall survival than placebo (6).

The following molecular rationale has been proposed to explain the differences in the response to pemetrexed according to histological type. Pemetrexed inhibits TS, as described above. However, the baseline expression of the TS gene is significantly higher in squamous cell carcinoma than in adenocarcinoma. Preclinical data suggest that high expression of TS is associated with reduced activity of pemetrexed (7).

S-1 is an oral anticancer drug that combines tegafur, a prodrug of 5-fluorouracil, with gimeracil and oteracil potassium. Gimeracil reversibly inhibits the rate controlling enzyme system responsible for the metabolism of 5-fluorouracil, thereby increasing concentrations of 5-fluorouracil in blood and enhancing its antitumour activity. Oteracil potassium reversibly inhibits the phosphorylation of 5-fluorouracil, thereby reducing its gastrointestinal toxicity (8, 9). A phase II study of S-1 monotherapy reported a response rate of 22% in patients with non-small cell lung cancer (10). Subsequently, 2 other phase II studies were performed in Japan to evaluate the efficacy and safety of combined chemotherapy with cisplatin and S-1 in patients with previously untreated, advanced non-small cell lung cancer. In the first study, cisplatin (60 mg/m^2) was given on day 8 ('day 8 study') (11). The response rate was 47.2%, and the median survival was 11.1 months. In the second study, cisplatin (60 mg/m^2) was given on day 1 ('day 1 study') (12). The response rate was 32.7%, and the median survival was 18.1 months. Two phase III studies of S-1 combined with platinum preparations are now in progress; the results are awaited.

S-1 acts primarily by inhibiting TS. Therefore, the antitumour activity of S-1 may depend on histological type, similar to pemetrexed. To explore whether the response to combined chemotherapy with cisplatin and S-1 depends on histological type, similar to pemetrexed, this study jointly analysed the results of two phase II studies of cisplatin plus S-1 in patients with previously untreated, advanced non-small cell lung cancer and compared treatment outcomes according to histological type (squamous cell carcinoma *vs.* non-squamous cell carcinoma).

Patients and Methods

Study design and subjects. This study analysed pooled data from 2 phase II clinical studies in which patients were enrolled from September 2000 through December 2005. The primary endpoints were progression-free survival and response rate; the secondary endpoint was overall survival. The numbers of patients who were enrolled or included in the full analysis set were 56 and 55 (respectively) in the day 8 study and 55 and 55 (respectively) in the day 1 study, the protocols of which are briefly described in the following section. The difference in the two studies is the administration schedule of CDDP and S-1. One patient in the day 8 study was ineligible and excluded. A total of 110 patients were thus included in the analysis. In both studies, eligible patients had to have a histopathologically confirmed diagnosis of stage IIIB or IV non-small cell lung cancer, measurable lesions, an age of 20 to 74 years, a performance status of 0 to 2 on the Eastern Cooperative Oncology Group scale, an expected survival of at least 3 months and adequately maintained organ function. Written informed consent was obtained from all patients before enrollment and the study protocol was approved by Institutional Review Boards at the participating centres. Both studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Treatment regimens. S-1 was supplied by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan) as 20- and 25-mg capsules. In the day 8 study, S-1 was given after meals on days 1 to 21, and cisplatin was given on day 8, followed by 2 weeks of rest. This 5-week cycle was repeated. In the day 1 study, cisplatin was given on day 1, and S-1 was given after meals on days 1 to 14, followed by 1 week of rest. This 3-week cycle was repeated. Cisplatin was administered according to the recommendations of the package insert. In both studies, the dose of cisplatin was 60 mg/m^2. The dose of S-1 was based on the patient body surface area (BSA) as follows: BSA<1.25 m^2, 80 mg/day; 1.25≤BSA<1.5 m^2, 100 mg/day; and BSA≥1.5 m^2, 120 mg/day.

Evaluation methods. Progression-free survival was defined as the period from the date of enrollment to the date on which disease progression was first confirmed (the date of evaluation). For patients who died before disease progression, death was attributed to disease progression. If there was no evidence of disease progression, the final day of evaluation was used to calculate progression-free survival. Response rates were evaluated according to the World Health Organisation criteria (13) in the day 8 study. In the day 1 study, response rates were assessed according to new guidelines for evaluating the treatment response of solid tumours (Response Evaluation Criteria in Solid Tumours guidelines) (14). Response rates were based on the combined total of complete responses (CR) and partial responses (PR). Overall survival was defined as the period from the date of enrollment to the date of death from any cause. Data on patients who were alive were censored on the last date on which the patient was confirmed to be alive. Data on patients who were lost to follow-up were censored on the date on which the patient was last confirmed to be alive, before being lost to follow-up. The incidences of adverse events were calculated according to version 2 of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (15).

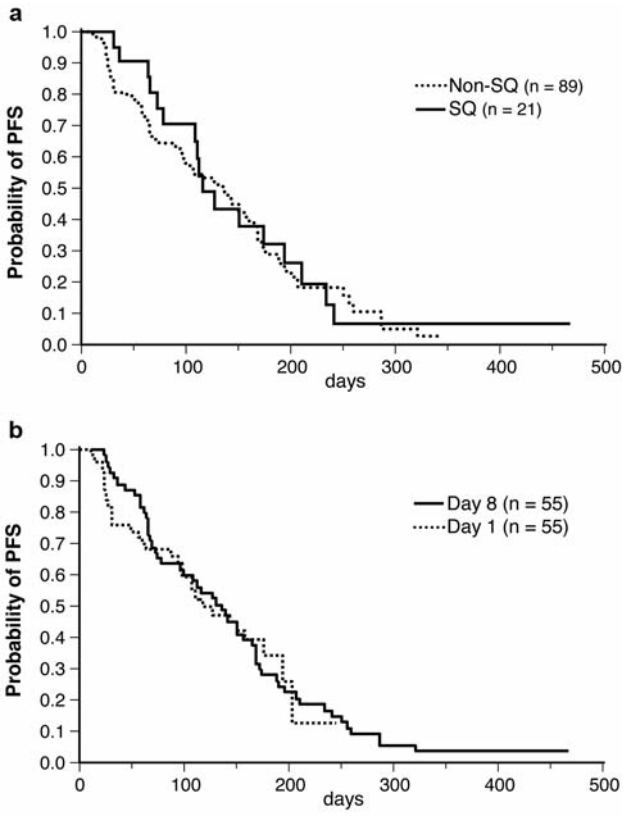

Figure 1. *a: Progression-free survival (PFS) according to histological type. b: Progression-free survival according to study. SQ: Squamous cell carcinoma.*

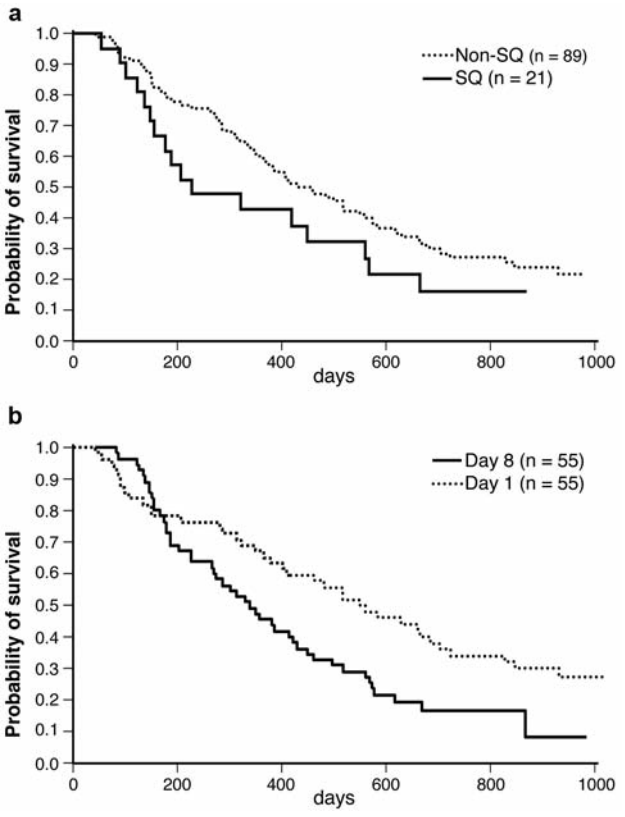

Figure 2. *a: Overall survival according to histological type. b: Overall survival according to study. SQ: Squamous cell carcinoma.*

Statistical analysis. Progression-free survival and overall survival curves were estimated by the method of Kaplan-Meier. Survival curves were compared between groups by the log-rank test. Response rates were compared by the Chi-squared test. Trial-stratified tests were also conducted after checking the assumption of common effect size across studies. A multiple Cox or logistic regression model including age, sex, performance score and clinical stage as well as histological type was applied according to whether a response variable was time-to-event or binary. All hazard ratios and odd ratios are reported with reference to patients who had a histological diagnosis of non-squamous cell carcinoma. Thus a hazard ratio >1 implies that patients with non-squamous cell carcinoma have better survival than those with squamous cell carcinoma, while an odds ratio >1 implies that patients with squamous cell carcinoma have a higher response rate than those with non-squamous cell carcinoma. All reported *p*-values are two-tailed. *P*-values <0.05 were considered to indicate statistical significance. All analyses were performed using SAS software ver. 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Demographic characteristics of patients. Of the 111 patients who were enrolled from September 2000 through December 2005, 110 received the protocol treatment, excluding 1 ineligible patient. Table I shows the demographic characteristics of the treated patients. Most patients (66.4%) were male, 80.9% had non-squamous cell carcinoma, 78.2% had stage IV disease, and 45.5% had a performance status of 0. Their median age was 61 years (range, 36 to 74 years). The median number of treatment courses was 4 in the day 1 study (range, 1 to 9) and 3 in the day 8 study (range, 1 to 12).

Progression-free survival and overall survival. Median progression-free survival according to histological type, on the basis of pooled data from both studies, was 3.8 months in patients with squamous cell carcinoma and 4.4 months in those with non-squamous cell carcinoma (hazard ratio, 0.91; 95% confidence interval [CI], 0.53 to 1.54; p=0.71) (Figure 1a). Median progression-free survival did not differ between the studies (Figure 1b) and trial-stratified analysis did not change the results (hazard ratio, 0.92; 95% CI, 0.54 to 1.57; p=0.75). Multivariate analysis also showed that there was no difference according to histological type (hazard ratio, 1.04; 95% CI, 0.59 to 1.86; p=0.86). The response rate according to histological type in the pooled data set was 47.6% (10 of 21 patients) in patients with squamous cell carcinoma and 38.2% (34 of 89

patients) in those with non-squamous cell carcinoma (odds ratio, 1.47; 95% CI, 0.56 to 3.83; p=0.43) (Table II). Similar results were obtained in trial-stratified analysis (odds ratio, 1.32; 95% CI, 0.49 to 3.52; p=0.59). Multivariate analysis also showed no apparent effect of histological type (odds ratio, 1.25; 95% CI, 0.45 to 3.47; p=0.67).

Median overall survival according to histological type in the pooled data set was 7.4 months in patients with squamous cell carcinoma and 14.1 months in those with non-squamous cell carcinoma (Figure 2a). However, the median overall survival was 18.1 months in the day 1 study as compared with only 11.1 months in the day 8 study (Figure 2b). The discrepancy in Figure 2a was caused by this between-trial difference in overall survival. The adjusted hazard ratio on trial-stratified analysis was 1.40 (95% CI, 0.82 to 2.40; p=0.22). The difference in survival between trials in Figure 2b may have been largely due to the post-protocol use of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI); EGFR-TKI was widely used in clinical practice in Japan at the time of the day 1 study, while no patient in the day 8 study received EGFR-TKI since it was not available at that time. However, due to the lack of detailed data, it was not possible to evaluate the difference.

Discussion

Many clinical studies have recently reported interactions between clinical characteristics and treatment outcomes in patients with non-small cell lung cancer. For example, a secondary analysis of data from the Iressa Survival Evaluation in Lung Cancer (ISEL) study, which compared gefitinib with placebo in previously treated patients, suggested that gefitinib is effective for subsets of patients with specific characteristics, such as adenocarcinoma, female sex, and nonsmoker status (16). In the Iressa Pan Asian Study (IPASS), which was recently performed in previously untreated patients, treatment outcomes differed according to the presence or absence of EGFR mutations (17). The Evaluation of Sorafenib, Carboplatin and Paclitaxel Efficacy in Non-small Cell Lung Cancer (ESCAPE) study, in which sorafenib was combined with carboplatin/paclitaxel in previously untreated patients, suggested that this regimen is less effective for squamous cell carcinoma (18).

Clinical trials have provided evidence that pemetrexed is more effective against adenocarcinoma than against non-adenocarcinoma, similar to molecular targeted agents. This difference in response may be attributed to the inhibition of TS, one of the mechanisms of action of pemetrexed. The lower expression rate of TS in adenocarcinoma in comparison to squamous cell carcinoma (19) provides a theoretical basis for the difference in treatment response.

Factors related to the response to such newly developed drugs for the treatment of non-small cell lung cancer have increasingly become clear. As described above, the response to several drugs has been shown to depend on histological type. Outcomes are gradually improving in patients with adenocarcinoma, but remain poor in patients with squamous cell carcinoma. The present pooled analysis indicated that the antitumour response to cisplatin plus S-1 does not depend on histological type. In contrast, overall survival differed according to histological type. This difference may be attributed to the following factors. In the day 1 study, many patients received EGFR-TKI after completion of the protocol treatment, whereas the day 8 study was performed before EGFR-TKI was approved. Overall survival was thus considerably better in the day 1 study than in the day 8 study. Another factor was that most patients in the day 1 study had non-squamous cell carcinoma. The prolongation of overall survival in the day 1 study may thus reflect the high proportion of patients with non-squamous cell carcinoma. However, this conclusion remains speculative because adequate follow-up data on the response to EGFR-TKI as subsequent treatment were not obtained.

The present analysis showed that progression-free survival does not differ according to histological type (squamous cell carcinoma *vs*. non-squamous cell carcinoma), in contrast to the results reported for pemetrexed. Although S-1 also inhibits TS, the mechanism involved differs from that of pemetrexed. 5-Fluorouracil derived from tegafur undergoes nucleic acid metabolism and is phosphorylated to 5-fluoro-2'-deoxyuridine 5'-monophosphate (FdUMP). FdUMP then reacts with reduced folate cofactors to form a ternary complex with TS, thereby inhibiting DNA synthesis. Apart from the metabolism of 5-fluorouracil by nucleic acids, resulting in cytocidal activity, most 5-fluorouracil is metabolised by dihydropyrimidine dehydrogenase (DPD), producing inactive molecules. S-1 contains gimeracil, which strongly and reversibly inhibits DPD, and has been experimentally shown to be less affected by DPD than conventional 5-fluorouracil derivatives (20). Orotate phosphoribosyl transferase (OPRT), a key enzyme that catalyses the first step in the phosphorylation of 5-fluorouracil by nucleic acids, has been suggested to have an important role in the antitumour activity of 5-fluorouracil. Ichikawa *et al*. reported that low TS expression and high OPRT expression are predictors of the response to S-1 (21). Nakano *et al*. immunohistologically evaluated the expression levels of TS and OPRT according to histological type, using surgically resected specimens of non-small cell lung cancer (22). They found that adenocarcinoma is associated with low TS expression/low OPRT expression, whereas squamous cell carcinoma is associated with high TS expression/high OPRT expression. Low expression of the target enzyme TS in adenocarcinoma is thus consistent with the theory that pemetrexed is effective against adenocarcinoma. With regard to the relation between the expression of these enzymes and the response to S-1, adenocarcinoma may respond well to S-1 because of the low

expression of these target enzymes, similar to pemetrexed. Although squamous cell carcinoma shows high expression of the target enzyme TS, the expression of OPRT, which catalyses the first step in phosphorylation of 5-fluorouracil, is also high. This high OPRT expression may account for the good response of squamous cell carcinoma to S-1. These mechanisms of action may explain the lack of a difference in the responses to S-1 between adenocarcinoma and squamous cell carcinoma.

Cisplatin and pemetrexed can be administered concurrently with thoracic radiotherapy. Clinical studies have reported a good response to this treatment regimen, and further clinical development is awaited. However, squamous cell carcinoma accounts for a high proportion of all locally advanced, stage III, non-small cell lung cancer cases for which a combination of chemotherapy and radiotherapy remains the standard treatment. The number of such patients who receive pemetrexed is limited because of its low efficacy for this type of lung cancer. Because S-1 acts as a radiosensitiser, a phase II study evaluated the combination of cisplatin plus S-1 and thoracic radiotherapy. This regimen was found to be safe and very effective for unresectable stage III non-small cell lung cancer (response rate, 87.5%; median progression-free survival, 13.4 months; median survival time, not reached) (23). Therefore, cisplatin plus S-1 is a new candidate for the standard treatment of advanced non-small cell lung cancer that can be combined with thoracic radiotherapy. An important advantage of this regimen is that response does not differ according to histological type and can therefore also be used to treat squamous cell carcinoma.

In conclusion, the results from the present study suggest that S-1 is well tolerated and effective regardless of histological type. However, at the present time there are insufficient data to evaluate this exploratory analysis. Further two phase III studies will help evaluate the histological efficacy of S-1. S-1 is therefore expected to be effective against non-squamous cell carcinoma as well as squamous cell carcinoma.

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