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A Randomized Phase III Trial of Oral S-1 plus Cisplatin versus Docetaxel plus Cisplatin in Japanese Patients with Advanced Non-small-cell Lung Cancer: TCOG0701 CATS TRIAL

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Abstract

Background: Platinum-based two-drug combination chemotherapy has been standard of care for patients with advanced non-small-cell lung cancer (NSCLC). The primary aim was to compare overall survival (OS) of patients with advanced NSCLC between the two chemotherapy regimens. Secondary endpoints included progression-free survival, response, safety, and quality of life (QOL).

Patients and methods: Patients with previously untreated stage IIIB or IV NSCLC, an ECOG PS of 0-1 and adequate organ function were randomized to receive either oral S-1 80 mg/m^2/day on days 1 to 21 plus cisplatin 60 mg/m^2 on day 8 every 4 to 5 weeks, or docetaxel 60mg/m^2 on day 1 plus cisplatin 80 mg/m^2 on day 1 every 3 to 4 weeks, both up to 6 cycles.

Results: 608 patients from 66 sites in Japan were randomized to S-1 plus cisplatin (n=303) or docetaxel plus cisplatin (n=305). OS for oral S-1 plus cisplatin was non-inferior to docetaxel plus cisplatin (median survival, 16.1 v 17.1 months, respectively; HR=1.013; 96.4% CI, 0.837-1.227). Significantly higher febrile neutropenia (7.4% v 1.0%), grade 3/4 neutropenia (73.4% v 22.9%), grade 3/4 infection (14.5% v 5.3%) and, grade 1/2 alopecia (59.3% v 12.3%) were observed in the docetaxel plus cisplatin than in the S-1 plus cisplatin. There were no differences found

in progression-free survival or response between the two arms. QOL data investigated by EORTC QLQ-C30 and LC-13 favored the S-1 plus cisplatin.

Conclusion: Oral S-1 plus cisplatin is not inferior to docetaxel plus cisplatin and is better tolerated in Japanese patients with advanced NSCLC.

Clinical Trial Number: UMIN000000608

Key words: advanced non-small-cell lung cancer, S-1, cisplatin, docetaxel, randomized trial

Key Message : Oral S-1 plus cisplatin is non-inferior to docetaxel plus cisplatin in terms of overall survival with favorable QOL data. S-1 plus cisplatin is an option for the first-line treatment of patients with advanced NSCLC.

INTRODUCTION

Lung cancer is the leading cause of cancer mortality in the United States, Europe and Japan. Although age-adjusted lung cancer mortality has been declining due to decreased tobacco consumption in industrialized countries, the disease is a growing problem in developing countries[1, 2]. Non-small-cell lung cancer (NSCLC) accounts for 85% of lung cancer, and most symptomatic patients have advanced disease at presentation. Platinum-based combination chemotherapy has been the mainstay of care for patients with stage III and IV NSCLC[3]. Molecularly targeted therapy, including tyrosine kinase inhibitors (TKIs), significantly improves QOL and prognosis of patients who harbor driver mutations, however, most patients who had response to TKIs had disease progression 9 to 10 months after start of the treatment and became candidates for cytotoxic chemotherapy[4-7]. Thus, improvement of combination chemotherapy is still a clinically meaningful strategy.

Docetaxel plus cisplatin (DP) is the only third-generation chemotherapy regimen that has demonstrated significant improvement in overall survival (OS) and quality of life (QOL) compared with vindesine plus cisplatin, a second-generation chemotherapy regimen, in patients with stage IV NSCLC in Japan[8]. A larger randomized trial comparing DP with vinorelbine plus cisplatin also demonstrated improved QOL and

OS, favoring DP[9]. Furthermore, a meta-analysis of docetaxel- and vinca alkaloid-based chemotherapy, mainly vinorelbine, revealed superior OS of docetaxel[10].

S-1 (TS-1®; Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is an oral fluoropyrimidine anticancer agent combining tegafur, gimeracil and oteracil potassium in a molar ratio of 1.0:0.4:1.0[11]. Single agent S-1 is active in NSCLC[12]. In a phase II trial of S-1 plus cisplatin (SP), in which cisplatin (60 mg/m^2) was given on day 8 and S-1 (80 mg/m^2) was given on days 1 to 21 every 4 to 5 weeks, a response of 47% and a median survival of 11 months were attained in 55 patients with advanced NSCLC[13]. A phase I/II trial of a triweekly regimen with S-1 for 14 days plus cisplatin on day 1 revealed that the recommended dose of cisplatin was 60 mg/m^2. Among 55 eligible patients treated at the recommended dose, a response was observed in 33% of patients, and the median survival time was 18.1 month [14]. This promising activity was demonstrated together with a more favorable toxicity profile than that of commonly used platinum two-drug combination regimens.

We conducted a randomized, open-label, phase III, non-inferiority trial that compared SP with DP. The primary aim of this study was to compare OS of patients with advanced NSCLC between the two regimens. QOL was also evaluated as a secondary

endpoint.

METHODS

Patients

All patients enrolled in this study had cytologically or histologically confirmed NSCLC, with stage IIIB or IV (TNM classification, 5th edition) or postoperative recurrence. Previous chemotherapy and thoracic radiotherapy of the primary lesion were not allowed. Other eligibility requirements included: Age of 20 years to 74 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function, measurable or evaluable lesion and an expected survival of at least 12 weeks. All patients provided written informed consent before enrollment in this study. The protocol was designed in accordance with the Declaration of Helsinki and ethical guidelines for clinical research and was approved by the institutional review boards at all participating institutions.

Randomization

Eligible patients were randomly assigned in a 1:1 ratio to receive either SP or DP at the Tokyo Cooperative Oncology Group (TCOG) registration center. Randomization was

conducted by fax and performed with a dynamic randomization schema after stratifying patients according to disease stage (stage IIIB, stage IV, or postoperative recurrence), sex (male or female), and histologic type (adenocarcinoma or non-adenocarcinoma).

Treatment

Patients assigned to the SP group received oral S-1 (80 mg/m^2) in 2 divided doses daily after meals on days 1 to 21 and cisplatin (60 mg/m^2) as an intravenous infusion on day 8, repeated every 4 to 5 weeks. The dose of S-1 was assigned according to body surface area (BSA) as follows: BSA less than 1.25 m^2, 80 mg/day; BSA 1.25 m^2 to less than 1.50 m^2, 100 mg/day; and BSA 1.5 m^2 or higher, 120 mg/day. Patients assigned to the DP group received an intravenous infusion of docetaxel (60 mg/m^2) and cisplatin (80 mg/m^2) on day 1, repeated every 3 to 4 weeks. In both treatment groups, patients received a minimum of 3 cycles until the onset of progressive disease or unacceptable toxicity. The maximal number of chemotherapy cycles was 6.

Baseline and treatment assessments

Pretreatment assessments included physical examination, complete blood count and serum chemistry; brain, chest, and abdominal computed tomography (CT) or magnetic

resonance imaging (MRI), bone scintigraphy or positron emission tomography (PET). Physical examination, complete blood and serum chemistry were performed weekly during the first cycle of chemotherapy and at least once before the start of the second and each subsequent cycle of chemotherapy. Scans or radiographs used to assess response were obtained every 4 to 6 weeks. Responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

OS was defined as the time from randomization to death from any cause. Progression-free survival (PFS) was defined as the time from randomization to either progressive disease or death, whichever came first. Time to treatment failure (TTF) was defined as the time from randomization to death, progressive disease, or cessation of treatment before completion, whichever came first. QOL was evaluated with the use of the European Organization for Research and Treatment for Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)[15] and a 13-item lung cancer-specific questionnaire module (EORTC QLQ-LC13). Patients responded to this questionnaire before starting the first cycle of treatment, 1 week after cisplatin administration during the first cycle of treatment, and on completion of 2 cycles of treatment.

Statistical analysis

The full analysis set (FAS) included all patients who received the study treatment at least once, were observed for survival, and did not violate the eligibility criteria. The safety analysis set was defined as all patients who received the study treatment at least once. The primary endpoint was OS. For the FAS, a Cox proportional-hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Survival curves were estimated using the Kaplan-Meier method. Secondary endpoints were PFS, TTF, overall response, adverse events, and QOL. It was assumed that the 1-year survival in the DP group would be 60%, and the non-inferiority margin was set at about 10%, which corresponds to a HR of 1.322. We decided this setting was justified considering the favorable toxicity profile of SP. Given a one-sided significance level of 0.025, a statistical power of 0.85, an enrollment period of 2.5 years, and a follow-up period of 2 years, 290 patients per treatment group would be required. The total target number of patients was therefore set at 600. Two pre-specified interim analyses were performed, one 2.5 years after the start of the study and the other 1 year after the completion of enrollment. For OS, adjustment for multiplicity was performed with a Lan–DeMets boundary and an O'Brien–Fleming–type alpha spending function. A

one-sided significance level was set at 0.018 for the final analysis. All reported P values are two-sided. The analysis results are reported as HRs with a 96.4% CI for OS or a 95% CI for PFS and TTF. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC). Data analyses were conducted by coauthors (MT and HM) at the Department of Clinical Medicine (Biostatistics and Pharmaceutical Medicine), Kitasato University School of Pharmacy.

RESULTS

Patient characteristics

608 patients were enrolled in the trial between April 2007 and December 2008 from 66 institutions in Japan, 303 patients in the SP group and 305 patients in the DP group. Two patients in the SP group and 8 in the DP group did not receive their assigned treatments. Safety was therefore assessed in 301 patients in the SP group and 297 in the DP group. Two patients in the DP group were subsequently found to be ineligible. The final number of subjects was therefore 301 in the SP group and 295 in the DP group (Supplementary Figure S1, available at *Annals of Oncology* online). The demographic characteristics of the patients did not differ between the two groups (Table 1).

Efficacy

The median survival time was 16.1 months in the SP group and 17.1 months in the DP group (HR, 1.013; 96.4% CI, 0.837 to 1.227) (Figure 1A). The upper limit of HR was lower than 1.322, the prespecified upper limit of the non-inferiority margin, demonstrating that SP was non-inferior to DP with regard to the primary endpoint of OS. The 1-, 2- and 3-year survivals were 62% (95% CI, 0.56-0.67), 33% and 20%, respectively, in the SP group, and 61% (95% CI, 0.55-0.66), 34% and 20%, respectively, in the DP group. The results of subgroup analyses of OS were similar to those of the primary analysis, and there were no significant differences between the groups (Supplementary Figure S2, available at *Annals of Oncology* online).

The median PFS was 4.9 months in the SP group and 5.2 months in the DP group (HR, 1.113; 95% CI, 0.945 to 1.311) (Figure 1B). The median TTF was 4.2 months in the SP group and 4.4 months in the DP group (HR, 1.088; 95% CI, 0.925 to 1.280). The overall response was 26.9% in the SP group (CR, 1 patient; PR, 77) and 31.3% in the DP group (CR, 2; PR, 87). The proportion of disease control was similar in the SP group (74.1%) and the DP group (76.4%). The mean of dose intensity of cisplatin was 11.47 mg/m^2/week and 15.13 mg/m^2/week in the SP and DP group, respectively.

Post-study treatment and treatment compliance are shown in supplementary

Appendix A1, available at *Annals of Oncology* online.

Safety

Grade 3 or 4 febrile neutropenia, leukopenia, and neutropenia were significantly less frequent in the SP group than in the DP group (Table 2). Grade 3 or 4 thrombocytopenia was significantly more frequent in the SP group. More grade 3 or 4 infection was observed in the DP group (14.5%) than in the SP group (5.3%). All grades of anorexia, nausea, vomiting, and hair loss were significantly less frequent in the SP group (Table 2). There was one treatment-related death in the SP group (suffocation due to vomiting).

QOL

Of 301 patients in the SP group and 295 patients in the DP group, 229 patients (76%) and 235 patients (80%), respectively, answered the questionnaires all three times. It was found as a primary measure of QoL that Global Health Status/QoL functioning was better in patients treated by SP than in those treated by cisplatin plus docetaxel. (p<.0001) (Figure 2A) Physical functioning was also better in SP. (p=.0058) Furthermore, good results for scale sores of Fatigue, Nausea and vomiting, Pain, Sleep disturbance, Appetite loss, and Diarrhea were obtained in the SP, and the difference in

QOL during treatment (1 week after the first dose of cisplatin) was particularly remarkable (Supplementary Figure S3, available at Annals of Oncology online). Interesting, QOL measured by the QLQ-LC13 was better in the SP group not only at the second measurement but also at the third measurement ($p<0.01$) (Figure 2B).

DISCUSSION

The present study showed that compared with DP, SP is non-inferior in terms of OS in patients with advanced NSCLC. As a result, one-, two-, and three-year survivals were similar between the two groups. Notably, QOL during chemotherapy favored SP. Response and PFS also did not differ between the two groups. Although interaction p-value by PS was 0.0494, subgroup analysis by PS was not significant between the two groups.

Before starting the study, we defined clinically meaningful adverse events such as neutropenic fever, neutropenia, infection, gastrointestinal toxicity and alopecia. Grade 3 or 4 of these toxicities were less frequent in the SP arm. Although there was no difference in the frequencies of grades 3 or 4 diarrhea between the two arms, it would be important to instruct patients to stop S-1 when they have grade 2 or higher diarrhea.

Although the dose intensity of cisplatin (11.47 mg/m^2/week) in SP group was 24.19%

lower than that (15.13 mg/m^2/week) in DP group, SP regimen showed similar efficacy to DP regimen in terms of PFS (HR, 1.113; 95% CI, 0.945 to 1.311), OS (HR, 1.013; 96.4% CI, 0.837 to 1.227). Because optimum dose intensity of cisplatin for patients with NSCLC has not been determined, the present data might be valuable for optimum dose and schedule of cisplatin in the future trial.

Based on the landmark, randomized trial conducted by Temel and colleagues[16], QOL should be an explicit priority for health care professionals throughout the course of advanced cancer care. A randomized trial of DP compared to vinorelbine plus cisplatin showed global QOL and the Lung Cancer Symptom Scale in favor of DP[9]. The favorable QOL data shown in the present trial of SP during chemotherapy were consistent with the less toxicity profile.

The present study contains some limitations: first, the non-inferiority margin of 1.322 in the study might be large. Actual one-year survival was 61% in the DP and 62% in the SP, and upper limit of HR was 1.227. The OS curves of both groups were almost identical. Second, EGFR mutation status or ALK rearrangement were not all evaluated. When the study started in 2007, EGFR TKIs were used only in patients with NSCLC previously treated with chemotherapy, and the EGFR testing was not common in this setting. The proportion of patients with EGFR mutation who received EGFR TKIs were

14% in the SP and 15.5% in the DP group. The data suggest that the conclusion of the study would not be biased by EGFR mutation status and TKIs treatment. Third, because of possible pharmacogenomic differences between Asian and Caucasian patients regarding chemotherapy efficacy and toxicity[17, 18], the results of the present study may not be applicable to Caucasian patients. The recommended dose of S-1 is lower in Caucasian patients than in Asian patients[19].

S-1 was compared to paclitaxel when these agents were combined with carboplatin in patients with advanced NSCLC. That trial also showed non-inferiority of S-1 plus carboplatin compared to paclitaxel plus carboplatin[20]. The introduction of newer-generation antiemetics such as aprepitant and palonosetron, and short hydration in chemotherapy containing cisplatin reduced chemotherapy-induced nausea/vomiting and renal toxicity[21] . Thus, it would be reasonable to use SP as a first-line chemotherapy based on the OS and favorable toxicity profile confirmed by the QOL data. Another large-scale trial comparing pemetrexed plus cisplatin to gemcitabine plus cisplatin also confirmed non-inferiority of pemetrexed plus cisplatin in patients with advanced NSCLC[22]. A subgroup analysis showed that pemetrexed plus cisplatin was more efficacious in patients with non-squamous NSCLC. After approval of pemetrexed for NSCLC in 2009, pemetrexed has been widely used as a first-line chemotherapy for

advanced non-squamous NSCLC in Japan. Such new data obtained after the start of the present trial could be potential obstacles to the acceptance of S-1 plus cisplatin as a standard first-line chemotherapy for advanced NSCLC.

In conclusion, SP is non-inferior to DP in terms of OS with favorable QOL data. SP is an option for the first-line treatment of patients with advanced NSCLC.

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