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A phase II study of cisplatin plus S-1 with concurrent thoracic radiotherapy for locally advanced non-small-cell lung cancer: The Okayama Lung Cancer Study Group Trial 0501☆

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ABSTRACT

Background: Although cisplatin-based chemotherapy combined with thoracic irradiation (TRT) is a standard treatment for unresectable, locally advanced non-small cell lung cancer (NSCLC), this treatment outcome has remained unsatisfactory. We had previously conducted a phase I trial of cisplatin plus S-1, an oral 5-fluorouracil derivative, and TRT, which were safe and effective.
Methods: In this phase II trial, 48 patients with stage III NSCLC received cisplatin (40 mg/m^2 on days 1, 8, 29 and 36) and S-1 (80 mg/m^2 on days 1–14 and 29–42) and TRT (60 Gy). The primary endpoint was the response rate.
Results: A partial response was observed in 37 patients (77%; 95% confidence interval: 63–88%). At a median follow up of 54 months, the median progression-free survival and median survival time were 9.3 and 31.3 months, respectively. No difference in efficacy was observed when the patients were stratified by histology. Toxicities were generally mild except for grade 3 or worse febrile neutropenia and pneumonitis of 8% and 4%, respectively. No patient developed severe esophagitis. At the time of this analysis, 35 (73%) of the 48 patients recurred; 15 (31%) showed distant metastasis, 17 (35%) had loco-regional disease, and 2 (4%) showed both loco-regional disease and distant metastasis.
Conclusions: This chemoradiotherapy regimen yielded a relatively favorable efficacy with mild toxicities in patients with locally advanced NSCLC.

☆ UMIN clinical trial registry: C000000079: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000000116&language=J.

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1. Introduction

Cisplatin (CDDP)-based chemotherapy combined with thoracic irradiation (TRT) is a standard treatment for unresectable, locally advanced non-small cell lung cancer (NSCLC), but the treatment outcomes have remained unsatisfactory with a 5-year survival rate of approximately 20–30% [1–3]. S-1 is a newly developed oral 5-fluorouracil derivative, possessing promising anti-tumor activity in NSCLC [4–7]. The CDDP and S-1 combination chemotherapy in the metastatic setting yields favorable antitumor activity with an overall response rate (ORR) of 47.3% and a median survival time (MST) of 11 months in a phase 3 trial [8]. Additionally, 5-fluorouracil, as well as CDDP, can sensitize cancer cells to radiotherapy (RT) [9]. Combined treatment with S-1 plus irradiation was significantly more effective against NSCLC xenografts than irradiation alone [10].

The activity of S-1, however, has been less extensively evaluated in the locally advanced setting [11–13]. We demonstrated safety profiles with dose-limiting toxicities of febrile neutropenia, thrombocytopenia, bacterial pneumonia and a delayed second cycle of chemotherapy but without severe radiation pneumonitis in a prior phase I trial of CDDP plus S-1 and concurrent TRT [3]. In that study, the preliminary overall response rate (ORR) was 86.4% with MST of 24.4 months. Based on these findings, we conducted subsequently a phase II trial of CDDP and S-1 combined concurrently with TRT, with the primary endpoint of ORR and the secondary endpoints of toxicities, treatment compliance, overall survival, and progression-free survival.

2. Patients and methods

2.1. Patient eligibility

The eligibility criteria are listed in Appendix Table A1. The staging work up included a chest radiograph, computed tomography scans of the chest and abdomen, magnetic resonance imaging of the brain, bronchoscopy and radionuclide bone scans if clinically needed. We regarded lymphnodes of which shorter diameter was ≥1.0 cm as the nodal involvement in the CT scan. Positron emission tomography was also performed in most of the patients, although the definition of PET positivity varied among the participating institutes. Staging was done based on the AJCC TNM staging system for lung cancer (6th edition, 2002).

The protocol was approved by the Institutional Review Board. All of the patients gave written informed consent before study entry (UMIN registration number: C000000079).

2.2. Treatment

The detailed planned administration schedule of chemoradiotherapy was defined in the previous phase I trial [3]. Briefly, patients received an oral dose of S-1 at a dose of 40 mg/m^2 twice daily from days 1 to 14 and 29 to 42. CDDP, 40 mg/m^2/day, diluted in 300 mL of physiological saline, was administered intravenously over a 1-h period on days 1, 8, 29, and 36 of each cycle. This split CDDP schedule was based on our prior phase I trial design [3] and the favorable efficacy data in the same split administration of CDDP when combined with docetaxel and concurrent TRT [1]. Each patient was also intravenously pre-medicated with dexamethasone (8 mg) and granisetron (3 mg) 30 min prior to CDDP injection.

Radiation, a single 2-Gy daily fraction for 5 consecutive days each week with a total dose of 60 Gy was administered from day 1 using a linear accelerator (4–10 MeV). The treatment scheme as to how radiotherapy was delivered was described in the prior report [3]. Briefly, the curative radiation field was traditionally defined using chest radiography and contrast-enhanced computed tomography. The initial planned radiation field did not exceed 50% of the ipsilateral lung. An additional 20-Gy dose was administered to boost the volume after an initial dose of 40 Gy. Although the way in which we defined the initial radiation field would be somewhat out-dated, this seemed the best way just in this study that could be achieved in the context of a multicentre study in which some community-based institutions had limited technological capacities. No systematic quality control among the institutes was not done.

Dose and schedule modification was also planned same as that in the phase I trial [3]. If patients developed grade 4 leukopenia or neutropenia or grade 3 febrile neutropenia, the planned S-1 administration was interrupted. For serum creatinine levels of 1.5–2.0 mg/dL and >2.0 mg/dL, S-1 administration was reduced to the half dose and halted, respectively. Regarding CDDP administration, it was withheld within if patients experienced grade 3 or worse hematologic toxicities on days 8 and 36, and delayed toxicities on day 29 if hematological toxicities ≥grade 2 and non-hematologic toxicities ≥grade 3. CDDP administration was withdrawn if the serum creatinine score was >2.0 mg/dL. Radiation therapy was interrupted with grade 4 hematologic toxicity, grade 3 or worse febrile neutropenia, grade 3 or 4 esophagitis, or a decrease in PaO2 >10 mmHg compared with the baseline.

2.3. Assessment of response and toxicity

The treatment response was evaluated according to the standard Response Evaluation Criteria in Solid Tumors and confirmed in a blinded central extramural review. Toxicity was assessed based on the Common Terminology Criteria for Adverse Events v3.0. Regarding the radiation pneumonitis, we assessed both acute and delayed toxicities.

2.4. Statistical consideration

The primary endpoint was set as the ORR. Assuming that an ORR of 75% in eligible patients would indicate potential usefulness, whereas a rate of 60% would be the lower limit of interest, with $\alpha = 0.1$ and $\beta = 0.20$, the estimated accrual number was 44 patients. The primary endpoint was considered to be met if 31 or more patients had an overall response at the final analysis. The interim analysis was preplanned, setting that this regimen would be rejected when 14 or less of the first 24 patients had an objective response and the additional enrollment would be discontinued. With an assumed dropout rate of approximately 10%, a total of 48 patients was required. The progression-free survival time and overall survival time, secondary endpoints, were calculated from the date of registration until the first documented date of disease progression or death, respectively, using the Kaplan–Meier method. All of the p values corresponded to two-sided tests, and statistical significance was set at a p value less than 0.05. Statistical analyses were conducted using STATA (ver. 11; StataCorp, College Station, TX, USA).

3. Results

3.1. Patients and treatment delivery

Between 2006 and 2009, 48 patients were registered in the present study. Table 1 lists their demographics, which were similar to those of patients recruited in the prior phase I trial [1]. FDG-PET scan was used for staging in 25 (52%) of the 48 patients, whilst the relevant data were not available in 6 patients. The mean ratios of the actual dose intensity divided by the projected dose intensity in CDDP and S-1 administration were 0.73 (range: 0.25–1.00) and 0.79 (range: 0.11–1.00), respectively (Fig. 1A and B). The radiation dose