Phase II study of S-1 and irinotecan combination therapy in EGFR-mutated non-small cell lung cancer resistant to epidermal growth factor receptor tyrosine kinase inhibitor: North Japan Lung Cancer Study Group Trial 0804 (NJLCG0804)

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Abstract
We conducted a multicenter phase II trial to evaluate the efficacy and safety of S-1 and irinotecan combination therapy in patients with epidermal growth factor receptor-mutated non-small-cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitors. Epidermal growth factor receptor-mutated non-small-cell lung cancer patients treated with epidermal growth factor receptor tyrosine kinase inhibitors and platinum-based chemotherapy received 80 mg/m² S-1 on days 1–14 and 70 mg/m² irinotecan on days 1 and 8 of a 21-day cycle. The primary endpoint was disease control rate 8 weeks after enrollment. The secondary endpoints were progression-free survival, overall response rate, and safety. We enrolled 25 patients from five hospitals. The patients underwent a median of four cycles. The disease control rate, 8 weeks after enrollment, was 84% (95% confidence interval 63.9–95.5%). Progression-free survival and overall survival were 5.0 and 17.1 months, respectively. The overall response rate was 52.0%. Grade ≥ 3 adverse events were reported in 56.0% of patients: hematological toxicities of leukopenia (44%), neutropenia (52%), anemia (20%), thrombocytopenia (20%), and febrile neutropenia (16%). Non-hematological toxicities of grade ≥ 3 included elevated alanine aminotransferase (4%), anorexia (8%), nausea (4%), diarrhea (16%), and pulmonary embolism (4%). None developed grade 5 toxicities. Combination therapy with S-1 and irinotecan in patients with epidermal growth factor receptor-mutated non-small-cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitors and platinum-based chemotherapy demonstrated high effectiveness with tolerable toxicities. Future phase III studies are needed to evaluate the role of this treatment in such patients.

Keywords Epidermal growth factor receptor · Non-small cell lung cancer · Combination therapy

Introduction
Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases, and most patients progress at the time of diagnosis. Additionally, the standard of care for such patients is chemotherapy [2]. Recently, targetable oncogenic drivers, such as those affecting epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS-1, v-raf murine sarcoma viral oncogene homolog B1 (BRAF), neutrophil tyrosine kinase receptor (NTRK), and rearranged during transfection (RET), have been identified in NSCLC. Moreover, the immune system against cancer and tumor microenvironment is better understood [3]. As a result, molecular-targeted therapies, such as EGFR tyrosine kinase inhibitors (TKIs) and
immune checkpoint inhibitors, have been developed, leading to a dramatic increase in survival among some patients with NSCLC; however, the prognosis for most remains poor [4].

Regarding advanced EGFR-mutated NSCLC, EGFR-TKIs are recommended as first-line treatment, and platinum doublet-based chemotherapy is often utilized after EGFR-TKIs. Moreover, treatment with docetaxel plus ramucirumab [5], nab-paclitaxel [6], docetaxel [7], pemetrexed [8], and S-1 [9] has shown significant improvement in overall survival (OS), and these drugs are often administered in clinical practice. However, the efficacy of these agents is unsatisfactory. Therefore, further treatment options for patients with EGFR-mutated NSCLC treated with EGFR-TKIs and platinum doublet-based chemotherapy are needed.

S-1 and irinotecan have been developed in Japan. S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is an oral fluoropyrimidine comprising a 1.0:0.4:1.0 molar ratio of tegafur, 5-chloro-2, 4-dihydroxyypyridine (CDHP), and potassium oxonate (OXO) [10]. Tegafur, an oral prodrug of 5-fluorouracil (5-FU), is gradually converted to 5-FU and, in combination with CDHP, increases 5-FU concentration in serum and tumor tissue. In a phase III study of S-1 versus docetaxel in patients with NSCLC previously treated with platinum-based chemotherapy, S-1 resulted in OS and progression-free survival (PFS) of 12.75 and 2.86 months, respectively [9]. For previously untreated patients with NSCLC, phase III trials of a combination of S-1 plus platinum agents demonstrated non-inferiority to docetaxel or paclitaxel plus platinum agents [11, 12].

Irinotecan is an inhibitor of DNA topoisomerase I and has been shown to be effective as a first-line treatment for NSCLC. The combination of irinotecan and other cytotoxic agents has proven effective in patients with NSCLC. For example, in a randomized phase III study of four regimens of platinum-doublet chemotherapy containing irinotecan plus cisplatin, the combination of irinotecan with cisplatin showed comparable efficacy to that of other platinum-doublet regimens and was considered a standard treatment for advanced NSCLC [13]. Because the antitumor activities of irinotecan differ from those of S-1, their combination is expected to be beneficial and has been proven to be highly effective against advanced gastric and colorectal cancers [14, 15].

Based on these reports, we previously conducted a phase I study and reported the results of S-1 combined with weekly irinotecan in patients previously treated for advanced NSCLC. We determined the recommended dose of S-1 and irinotecan to be 80 and 70 mg/m², respectively [16]. Although patients with EGFR-mutated NSCLC did not show sensitivity to 5-FU in adjuvant chemotherapy [17], S-1 is effective for EGFR-mutated NSCLC cell lines in combination with gefitinib, resulting in the downregulation of thymidylate synthase [18]. Moreover, approximately half of the resistance mechanisms of first- or second-generation EGFR-TKIs comprised an additional T790M mutation [19]. The sensitivity to FU increases when both exon21 mutation and T790M are present, compared to that when only exon21 mutation is present in vitro [17], and the combination of EGFR-TKIs with S-1 synergistically inhibited the proliferation of T790M-positive NSCLC cells in vitro [20].

According to these insights, patients who are insensitive to EGFR-TKI treatment may be sensitive to S-1. For this reason, we conducted a multicenter phase II study to evaluate the efficacy and safety of the combination of S-1 and irinotecan in patients with EGFR-mutated NSCLC previously treated with EGFR-TKIs.

**Patients and methods**

**Patient eligibility**

The criteria for patient eligibility were as follows: (i) cytologically or histologically confirmed NSCLC classified as either inoperable or postoperative recurrence; (ii) harboring EGFR mutations detected by peptide nucleic acid (PNA)-locked nucleic acid (LNA) PCR clamp assay or PCR-Invader assay; (iii) previously treated with both platinum-based chemotherapy and EGFR-TKIs; (iv) confirmed disease progression during EGFR-TKI treatment; (v) no treatment between EGFR-TKI therapy and initiation of the study; (vi) ≤ 2 regimens of cytotoxic agents, including postoperative adjuvant chemotherapy; (vii) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; (viii) adequate organ functions defined as a white blood cell (WBC) count of ≥ 3000/mm³, neutrophil count of ≥ 1500/mm³, platelet count of ≥ 100,000/mm³, hemoglobin level of ≥ 9.0 g/dl, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤ 2.5 times the upper normal limit; (ix) serum bilirubin concentration of ≤ 1.5 mg/dl; (x) serum creatinine concentration of ≤ 1.2 mg/dl; (xi) measured or calculated creatinine clearance rate of ≥ 60 ml/min; (xii) partial pressure of arterial oxygen of ≥ 60 torr or a peripheral oxygen saturation of ≥ 95%; and (xiii) provided informed consent.

The main exclusion criteria were (i) obvious interstitial pneumonia on chest X-ray; (ii) active concomitant cancer; (iii) clinically significant heart disease; (iv) uncontrolled diabetes mellitus and hypertension; (v) severe infection, diarrhea, intestinal paralysis, or intestinal obstruction; (vi) massive pleural or pericardial effusion or ascites requiring drainage; (vii) symptomatic brain metastasis; (viii) previous treatment with 5-FU or irinotecan; (ix) pregnant or lactating; (x) history of drug allergy; and (xi) other clinically significant complications or judged to be inappropriate by the investigators. The study protocol was approved.
by the institutional ethics committee at each participating institution.

**Study design and treatment**

This was a multicenter, open-label, single-arm, phase II study. The primary endpoint of this study was the disease control rate (DCR) at 8 weeks after enrollment, and the secondary endpoints were PFS, overall response rate (ORR), and safety. The sample size was determined using 30% of the threshold 8-week DCR and 60% of the estimated 8-week DCR with a $\alpha$ error of 0.05 and a power of 0.9. Thus, the estimated minimum sample size was 23 patients. Allowing for a patient ineligibility rate of 10%, we planned to enroll 25 patients.

Based on the results of our phase I study [16], we used 70 mg/m² irinotecan combined with 80 mg/m² S-1. Although in the phase I study, patients received S-1 on days 1–14 and irinotecan on days 1, 8, and 15 of each 28-day cycle, the infusion could not be administered on day 15 due to side effects in some cases. Because it is customary to administer irinotecan on days 1 and 8 of each 21-day cycle for colorectal and gastric cancer, we followed the same administration schedule for irinotecan and administered S-1 twice after meals on days 1–14 of each 21-day cycle. The S-1 dose was determined according to body surface area (BSA) as follows: 80 mg/day for patients with a BSA of < 1.25 m², 100 mg/day for those with a BSA of 1.25–1.5 m², and 120 mg/day for those with a BSA of ≥ 1.5 m². Irinotecan was administered at a dose of 70 mg/m² on days 1 and 8. Treatment courses were repeated for at least four cycles every 21 days, and patients were administered more than five cycles according to the judgment of the investigators.

The starting criteria were as follows: WBC count of ≥ 3000/mm³, neutrophil count of ≥ 1500/mm³, platelet count of ≥ 100,000/mm³, AST and ALT levels of ≤ 2.5 times the upper normal limit, serum bilirubin concentration of ≤ 1.5 mg/dl, serum creatinine level under the upper normal limit of the institution, absence of infectious symptoms, and non-hematological toxicities of grade 1 or lower except nausea, vomiting, and general malaise. During the course of treatment, the administration of both S-1 and irinotecan was continued with the following criteria: WBC count of ≥ 2000/mm³, neutrophil count of ≥ 1000/mm³, platelet count of ≥ 75,000/mm³, AST and ALT levels of 2.5 times the upper normal limit, serum bilirubin concentration of ≤ 1.5 mg/dl, serum creatinine level below the upper normal limit, and grade 1 or lower non-hematological toxicities except nausea, vomiting, and general malaise. If the criteria were not satisfied, the administration was discontinued. The doses of both S-1 and irinotecan were reduced in the event of any of the following toxicities during the previous treatment cycle: WBC count of < 1000/mm³, neutrophil count of < 500/mm³, neutrophil count of < 1000/mm³, a body temperature of > 38 °C for 72 h under the use of granulocyte colony-stimulating factor, the incidence of grade 3 or higher peripheral neuropathy, or incidence of grade 3 or higher non-hematological toxicities except nausea, vomiting, alopecia, or general malaise.

During the first reduction, the S-1 dose was reduced from 120 to 100 mg/day, 100 to 80 mg/day, and 80 to 50 mg/day according to BSA, respectively, and the irinotecan dose was not reduced. During the second reduction, the S-1 dose was reduced from 100 to 80 mg/day, 80 to 50 mg/day, and 50 to 40 mg/day according to BSA, and the irinotecan dose was reduced from 70 to 60 mg/m². Patients could undergo two reductions before discontinuing treatment.

**Evaluation**

Tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors guidelines, version 1.0. Tumors were measured using computed tomography within 4 weeks before enrollment, 8 weeks after enrollment, and then every 6 weeks until disease progression. Partial and complete responses were confirmed at least 4 weeks after their initial recognition. PFS was defined as the time from enrollment until objective tumor progression was observed through CT, obvious clinical exacerbation, or death. OS was defined as the time from enrollment until death from any cause. PFS and OS were estimated using the Kaplan–Meier method. Toxicities were graded according to the Common Terminology Criteria for Adverse Events v.3.0. Finally, clinical and laboratory examinations were conducted at every administration of chemotherapy.

**Results**

**Patient characteristics**

Between February 2009 and April 2012, 25 patients (5 males and 20 females) from 5 institutions were enrolled in this study. The characteristics of the enrolled patients are summarized in Table 1. The median age was 62 (range 53–78) years. The ECOG PS was 0 in 4 patients and 1 in 21 patients. Regarding histological analysis, 23 patients (92%) had adenocarcinoma, 1 (4%) had adenosquamous cell carcinoma, and 1 (4%) had squamous cell carcinoma. Additionally, 5 patients (20%) were diagnosed as stage III, 13 (52%) as stage IV, and 7 (28%) had a postoperative recurrence. The type of EGFR mutation was Del19 in 17 patients and L858R in 8 patients (Table 1).
Response and survival

Patients received a median of four treatment cycles (range 1–12), and 21 patients were administered more than four cycles as specified in the protocol. A total of 130 cycles of chemotherapy were administered. Furthermore, protocol treatment was terminated in three patients before completing four cycles. Among the three patients, treatment was discontinued in two patients due to disease progression and one due to unacceptable toxicities. Among all 25 patients, the reasons for discontinuation were the completion of the protocol in 10 patients, progressive disease in 10 patients, toxicities in 2 patients, and being judged to be unsuitable by the investigators in 2 patients. One patient was undergoing treatment at the data cut-off date. The mean relative dose intensities of S-1 and irinotecan were 85.9 and 92.9%, respectively. Dose reduction was observed in seven patients due to diarrhea, neutropenia, anorexia, and stomatitis.

All patients were evaluated for their response to treatment. None of the patients had a complete response, 13 had a partial response, and 8 had stable disease. The resulting ORR and DCR at 8 weeks after enrollment were 52.0% (95% CI 31.3–72.2%) and 84.0% (95% CI, 63.9–95.5%), respectively. Thus, the lower limit of the DCR 95% CI was higher than the threshold DCR of 30% and the primary endpoint was met. 10 patients experienced disease progression (Table 2).

The final data cut-off date was November 2012, with a median follow-up time of 11.7 (range 5.6–28.1) months. The median PFS was 4.9 months (95% CI 4.1–6.3) and no patient had been treated for more than a year (Fig. 1a). The median OS was 16.8 months (95% CI 11.6–27.7) (Fig. 2a) and the 1-year and 2-year survival rates were 69.8% (95% CI 44.2–85.4%) and 28.6% (95% CI 9.3–51.7%), respectively. No correlation with the type of EGFR mutation was found (Figs. 1b and 2b).

Toxicity

The toxicity profiles of the patients are summarized in Table 3. The most frequent grade 3 or 4 hematologic toxicities were leukopenia (11 patients, 44%) and neutropenia (13 patients, 52%). Four patients (16%) experienced febrile neutropenia. Grade 3 or 4 thrombocytopenia was less frequent. Non-hematological toxicities were mostly mild. Nevertheless, the grade 3 or 4 non-hematological toxicities were diarrhea (4 patients, 16%), anorexia (2 patients, 8%), nausea (1 patient, 4%), elevated ALT (1 patient, 4%), and pulmonary embolism (1 patient, 4%).

Treatment administration was delayed in 10 patients (40%) due to neutropenia, diarrhea, anorexia, and elevated ALT. Two patients discontinued treatment due to neutropenia and diarrhea.

Discussion

We evaluated the efficacy and safety of S-1 combined with weekly irinotecan in patients with EGFR-mutated NSCLC previously treated with both EGFR-TKIs and platinum-based chemotherapy. EGFR-TKIs and platinum doublet-based chemotherapy are key treatments for patients with EGFR-mutated NSCLC. However, its effectiveness is limited, and new treatment options are necessary. This study showed

| Table 1 Patient characteristics |
|-----------------|-----------------|
| Characteristics  | No. of patients  |
| Total enrolled   | 25              |
| Median age, year (range) | 62 (53–78) |
| Sex              |                 |
| Male             | 5 (20%)         |
| Female           | 20 (80%)        |
| Performance status (ECOG) |     |
| 0                | 4 (16%)         |
| 1                | 21 (84%)        |
| Histology        |                 |
| Adenocarcinoma   | 23 (92%)        |
| Adenosquamous cell carcinoma | 1 (4%) |
| Squamous cell carcinoma | 1 (4%) |
| Stage            |                 |
| III              | 5 (20%)         |
| IV               | 13 (52%)        |
| Post-op recurrence | 7 (28%)     |
| EGFR mutation    |                 |
| exon 19 deletion (Del19) | 17 (68%) |
| exon 21 point mutation (L858R) | 8 (32%) |
| No. of prior treatment |     |
| 2                | 22 (88%)        |
| 3                | 3 (12%)         |
| Previous EGFR-TKI|                |
| Gefitinib        | 22 (88%)        |
| Erlotinib        | 3 (12%)         |

| Table 2 Overall response to treatment |
|---------------------------------------|
| Response                              | No. of patients (%) |
| Complete response                     | 0 (0%)              |
| Partial response                      | 13 (52%)            |
| Stable disease                        | 8 (32%)             |
| Progressive disease                   | 4 (16%)             |
| Overall response rate                 | 52.0% (95% CI 31.3–72.2) |
| Disease control rate                  | 84.0% (95% CI 63.9–95.5) |
| 8-week disease control rate           | 84.0% (95% CI 63.9–95.5) |
an ORR of 52.0%, which was higher than that reported in previous studies involving patients with NSCLC treated with platinum-doublet chemotherapy [5–9]. We observed an 8-week DCR of 84.0% (95% CI 63.9–95.5%), which met the primary endpoint. The PFS (4.9 months) and OS (16.8 months) found in this study are comparable to those reported previously, and the 1-year survival rate was 69.8%.

Several trials of combination therapy with S-1 and irinotecan for patients with NSCLC have been conducted, including our previous phase I study [16]. In the pretreatment setting, the PFS and OS range was 3–4 and 12–15 months, respectively [21–24], and the ORR was 6–15%. Although we cannot directly compare the PFS, OS, and ORR of these trials, our results were slightly higher. Additionally, the irinotecan and S-1 doses of 60–90 and 40–80 mg/m² in these trials are consistent with those in our trial. Regarding the eligibility of patients, these trials included patients with NSCLC, and this study included only those with EGFR-mutated NSCLC. It has been reported that cytotoxic chemotherapy agents are more effective for patients with EGFR-mutated NSCLC than those without EGFR mutations. In the IPASS study, which compared the efficacy of gefitinib and carboplatin–paclitaxel in advanced pulmonary adenocarcinoma patients, the PFS of chemotherapy was favorable in EGFR-mutated patients, and the ORR was higher in these patients than in those without EGFR mutations (46.4% and 23.5%, respectively) [25].

![Graph](image-url)

**Fig. 1** Kaplan–Meier curves of progression-free survival for all 25 treated patients (a) and classified by subtype of EGFR mutation (b)

![Graph](image-url)

**Fig. 2** Kaplan–Meier curves of overall survival for all 25 treated patients (a) and classified by subtype of EGFR mutation (b)
Additionally, the toxicities observed in this study were relatively high, which should be considered in the next phase of treatment. Outpatient treatment is preferred to improve QoL further. Moreover, the goal of therapy for these patients cannot be cured; thus, the increased rate of this toxicity was expected.

Regarding safety, hematological toxicity was observed relatively frequently. The incidence of grade 3 or 4 neutropenia and febrile neutropenia was 52 and 16%, respectively, and grade 3 or 4 anemia and thrombocytopenia were observed in 20 and 4% of the patients, respectively. These toxicity profiles were slightly higher than those in a previous report of S-1 plus irinotecan, and the incidence of grade 3 or 4 hematological toxicities was similar to that observed in patients treated with docetaxel [5–9]. Furthermore, the most common grade 3 or 4 non-hematological toxicity was diarrhea (16%). Both irinotecan and S-1 are prone to cause diarrhea; thus, the increased rate of this toxicity was expected. However, the rate of grade 3 or 4 diarrhea observed in our patients was only slightly higher than that in patients treated with irinotecan monotherapy (16 vs. 15%) [26]. The administration of this combination must be performed with care due to the possibility of diarrhea, vomiting, and anorexia.

The present study has several limitations. First, since this study was conducted with a small sample size, future studies will be needed to verify the promising effects of this regimen. Second, the present study lacked a quality-of-life (QoL) assessment. Most patients with advanced NSCLC cannot be cured; thus, the goal of therapy for these patients is to prolong survival with satisfactory QoL. Moreover, outpatient treatment is preferred to improve QoL further. Additionally, the toxicities observed in this study were relatively high, which should be considered in the next phase of treatment. In conclusion, we found that combination therapy with oral S-1 (80 mg/m² on days 1–14) and weekly irinotecan (70 mg/m² on days 1 and 8) showed promising efficacy against EGFR-mutated NSCLC with manageable toxicity. This regimen may be a useful treatment option for patients with advanced EGFR-mutated NSCLC resistant to EGFR-TKIs. Further phase III studies are warranted to verify the efficacy of this modified regimen.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Atsushi Nakamura received honoraria from MSD and Eli Lilly and Company. Akira Inoue received honoraria from Taiho Pharmaceutical. Shunichi Sugawara received honoraria from Taiho Pharmaceutical. The other authors declare no conflicts of interest.

Consent for publication Our manuscript is sufficiently anonymized.

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