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Switch maintenance chemotherapy using S-1 with or without bevacizumab in patients with advanced non-small cell lung cancer: a phase II study

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ABSTRACT

Objectives: We conducted this single-institute; prospective, non-randomized parallel two-arm phase II study to evaluate the efficacy and safety of switch maintenance chemotherapy with S-1 after induction therapy with a platinum-based regimen in patients with advanced non-small cell lung cancer (NSCLC).
Patients and methods: Patients not showing disease progression after induction platinum-based chemotherapy received S-1 at the dose of 40 mg/m^2 twice daily for 14 consecutive days, every three weeks, with or without bevacizumab (Bev) at the dose of 15 mg/kg. In cases where the induction chemotherapy regimen contained Bev, Bev was used as continuation maintenance chemotherapy where appropriate. The efficacy/toxicity of switch maintenance chemotherapy with S-1 and S-1 + Bev was evaluated separately. The primary end point of this study was the treatment success rate at three months after the start of S-1 treatment.
Results: Between July 2010 and January 2014, 79 patients were enrolled, of which 78 were found to be eligible for inclusion in this study. The treatment success rate at three months was 28.2% (90% confidence interval (CI), 7.1–17.1%) in the S-1 group and 64.1% (90% CI, 50.0–76.8%) in the S-1 + Bev group. The primary endpoint was met in the S-1 + Bev group. The median PFS and OS were 2.6 months and 11.0 months in the S-1 group, and 4.6 months and 19.9 months in the S-1 + Bev group, respectively. The most common grade three toxicity was neutropenia (10% incidence in the S-1 + Bev group). There were no cases of febrile neutropenia.
Conclusions: Switch maintenance chemotherapy with S-1 in combination with continuation maintenance chemotherapy with bevacizumab yielded modest efficacy with mild and acceptable toxicities.

1. Introduction

Platinum-based chemotherapy is established as the standard treatment for patients with advanced non-small cell lung cancer (NSCLC), especially in those with tumors that are negative for both sensitizing EGFR mutations and ALK [1]. In NSCLC patients with tumors harboring sensitizing EGFR mutations or expressing ALK fusion, platinum-based chemotherapy is one of the second-line treatment options after first-line treatment with a tyrosine-kinase inhibitor [2,3]. In some recently conducted randomized controlled studies, switch maintenance chemotherapy with pemetrexed or erlotinib prolonged the overall survival (OS) in patients with advanced NSCLC who did not show disease progression after four cycles of platinum-based chemotherapy [4,5].

S-1 is an oral anticancer agent consisting of tegafur (FT), 5-chloro-2, 4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo), mixed at the molar ratio of 1:0.4:1. In a phase II trial, S-1 monotherapy used as first-line treatment yielded a response rate of 22% in patients with advanced NSCLC [6]. Two phase III trials have demonstrated that S-1 plus carboplatin (CBDCA) or cisplatin (CDDP) was non-inferior, in terms of the OS, as compared to paclitaxel (PTX) plus CBDCA or docetaxel (DOC) plus CDDP, in patients with advanced NSCLC [7,8]. Furthermore, a phase II trial of S-1 monotherapy for pretreated patients with NSCLC reported a response rate of 19%, median progression-free survival (PFS) of 3.4 months, and median OS of 12.1 months [9]. Based on these reports,

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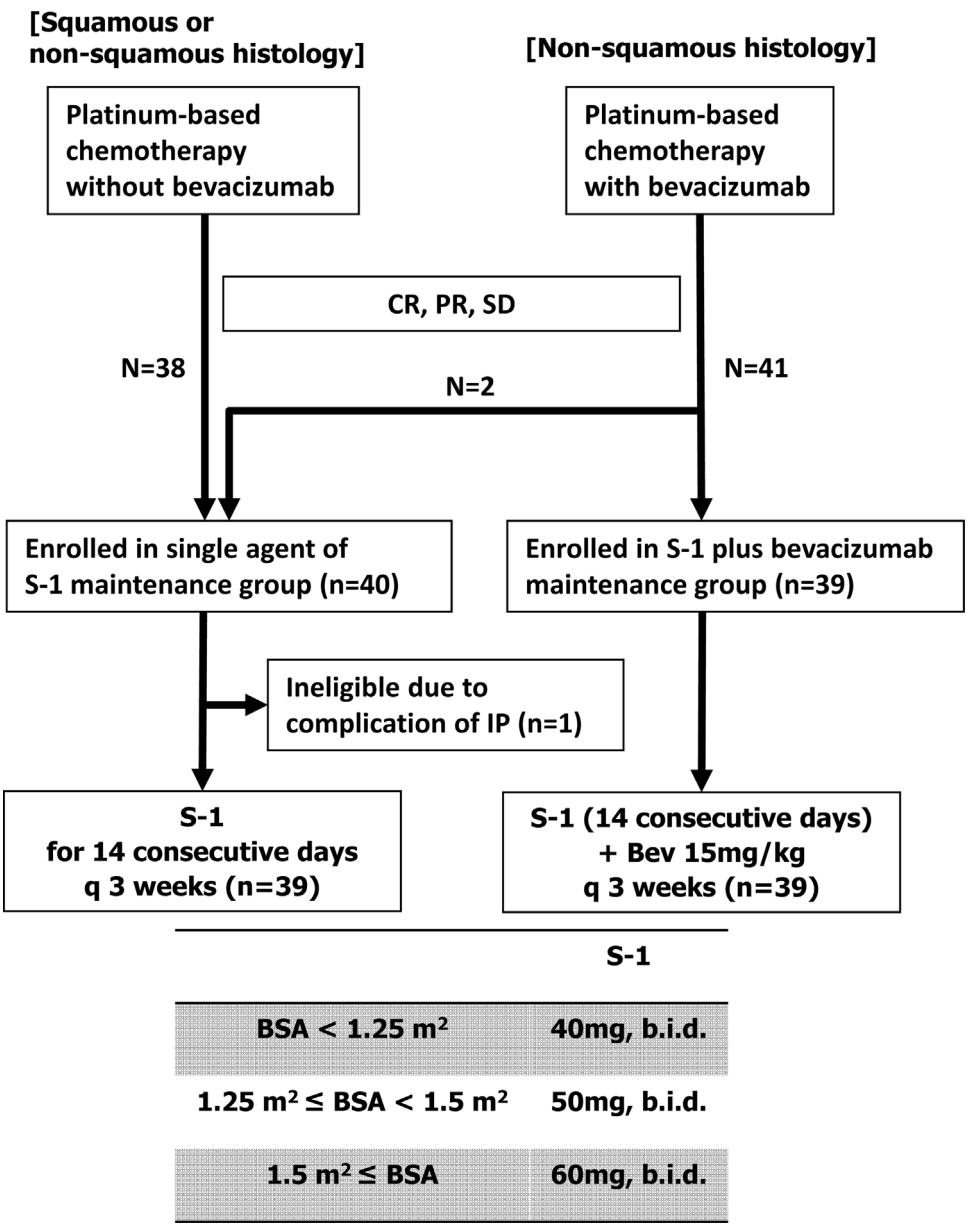

Fig. 1. Study design and CONSORT diagram. IP: interstitial pneumonia; BSA: body surface area.

we conducted a phase II trial of switch maintenance chemotherapy with S-1 after induction platinum-based chemotherapy in patients with advanced NSCLC.

2. Patients and methods

2.1. Study design

This trial was designed as a single-institute, prospective, non-randomized, parallel two-arm phase II study. We set two study treatment groups; the S-1 group and the S-1 plus bevacizumab (S-1 + Bev) group, because continuation maintenance chemotherapy with bevacizumab is a standard treatment in patients not showing disease progression after induction chemotherapy with a platinum-based regimen containing bevacizumab and it was thought that administration of bevacizumab in combination with S-1 might enhance the efficacy of S-1 [10,11]. Therefore, we evaluated the efficacy/toxicity of switch maintenance chemotherapy with S-1 or S-1 + Bev separately (Fig. 1). Even if the induction platinum-based chemotherapy contained bevacizumab, patients were permitted to enter the S-1 alone group if continuation maintenance therapy with bevacizumab was not feasible because of toxicity.

2.2. Eligibility criteria

Patients were required to have histologically of cytologically confirmed stage IV NSCLC. Patients with recurrent disease after surgical resection were also eligible. Other criteria included: (1) age between 20 and 74 years; (2) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; (3) response to induction platinum-based chemotherapy (3–4 cycles) classified as complete response (CR), partial response (PR) or stable disease (SD); (4) at least 3–7 weeks from the last treatment day of induction platinum-based chemotherapy; (5) adequate organ functions (i.e., total bilirubin $\leq$ 1.2 mg/dL, AST and ALT $\leq$ 100 U/L, serum creatinine $\leq$ 1.5 mg/dL, leukocyte count 4000–12,000/mm^3, neutrophil count $\geq$ 2000/mm^3, hemoglobin $\geq$ 9.0 g/dL, platelet count $\geq$ 100,000/mm^3, and PaO_2 on room air $\geq$ 70 mmHg or SpO_2 on