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A phase I trial of afatinib and bevacizumab in chemo-naïve patients with advanced non-small-cell lung cancer harboring EGFR mutations: Okayama Lung Cancer Study Group Trial 1404

Takashi Ninomiya[a,*], Naoyuki Nogami[b], Toshiyuki Kozuki[b], Daijiro Harada[b], Toshio Kubo[a,c], Kadoaki Ohashi[d], Shoichi Kuyama[e], Kenichiro Kudo[e], Akihiro Bessho[f], Nobuaki Fukamatsu[f], Nobukazu Fujimoto[g], Keisuke Aoe[h], Takuo Shibayama[i], Keisuke Sugimoto[j], Nagio Takigawa[k], Katsuyuki Hotta[l], Katsuyuki Kiura[a]

[a] Department of Respiratory Medicine and Allergy, Okayama University Hospital, 2-5-1, Shikata-cho, Okayama, Japan
[b] Department of Thoracic Oncology and Medicine, National Hospital Organization, Shikoku Cancer Center, 160, Minamiumemoto-ko, Matsuyama, Japan
[c] Center for Oncology, Okayama University Hospital, 2-5-1, Shikata-cho, Okayama, Japan
[d] Department of Hematology, Oncology and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1, Shikata-cho, Okayama, Japan
[e] Department of Respiratory Medicine, Iwakuni Clinical Center, 1-1-1, Atago-cho, Iwakuni, Japan
[f] Department of Respiratory Medicine, Japanese Red Cross Okayama Hospital, 2-1-1, Aoe, Okayama, Japan
[g] Department of Medical Oncology, Okayama Rosai Hospital, 1-10-25, Chikkomidorimachi, Okayama, Japan
[h] Department of Medical Oncology, National Hospital Organization, Yamaguchi-Ube Medical Center, 685, Higashikiwa, Ube, Japan
[i] Department of Respiratory Medicine, National Hospital Organization, Okayama Medical Center, 1711-1, Tamasu, Okayama, Japan
[j] Department of Respiratory Medicine, Japanese Red Cross Kobe Hospital, 1-3-1, Wakihamakaigann-dori, Chuo-ku, Kobe, Japan
[k] Department of General Internal Medicine 4, Kawasaki Medical School, 2-6-1, Nakasange, Okayama, Japan
[l] Center for Innovative Clinical Medicine, Okayama University Hospital, 2-5-1, Shikata-cho, Okayama, Japan

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ABSTRACT

Objective: In advanced epidermal growth factor receptor (EGFR)-mutant non-small-cell lung cancer (NSCLC), treatment with afatinib, a second-generation EGFR-tyrosine kinase inhibitor (TKI), confers a significant survival benefit over platinum-based chemotherapy. The first-generation EGFR-TKIs gefitinib and erlotinib in combination with bevacizumab have improved progression-free survival. We hypothesized that the combination of afatinib with bevacizumab would further improve efficacy, and conducted a phase I trial to test this hypothesis.
Materials and methods: Untreated patients with advanced EGFR-mutant NSCLC were enrolled. The primary endpoint was safety. Two doses of afatinib, 40 mg/day (level 0) and 30 mg/day (level −1), were evaluated in combination with 15 mg/kg bevacizumab every 3 weeks. Optimal dosing was determined by dose-limiting toxicity (DLT), with the concentration at which ≤4 of 12 patients experienced toxicity considered the recommended dose.
Results: Nineteen patients were enrolled (level 0:5, level −1:14). Three of the five patients at level 0 experienced a DLT, which indicated that this dose was unfeasible. Three patients at level −1 developed a DLT of grade 3 non-hematological toxicity, which was soon resolved. Grade 3 or worse adverse events were experienced by all five patients at dose level 0 (diarrhea in 2, skin rash in 1, hypoxia in 1, and paronychia in 1), and by three patients at level −1 (diarrhea in 2 and anorexia in 1). Among 16 evaluable patients, 1 had a complete response, 12 had partial responses, and 0 had progressive disease.
Conclusion: Afatinib plus bevacizumab (level −1) was well tolerated and showed evidence of favorable disease control. This combination therapy may represent a potent therapeutic option for patients with EGFR-mutant NSCLC.

* Corresponding author at: Department of Respiratory Medicine and Allergy, Okayama University Hospital, 2-5-1, Shikata-cho, Okayama, 700-8558, Japan.
E-mail address: tninomiya5@okayama-u.ac.jp (T. Ninomiya).

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1. Introduction

Lung cancer is a leading cause of death worldwide. The major pathological subtype of lung cancer is non-small-cell lung cancer (NSCLC); in some NSCLCs, activating mutations in the epidermal growth factor receptor (EGFR) gene have been reported [1]. In this subgroup of patients, an EGFR-tyrosine kinase inhibitor (EGFR-TKI) was found to prolong progression-free survival (PFS) compared with standard platinum-based chemotherapy [2–7]. While the median overall survival (OS) of this patient subgroup reaches almost 2 years with EGFR-TKI treatment, this is still insufficient. To prolong PFS and OS, more effective treatments are needed.

Afatinib, a second-generation EGFR-TKI, is an irreversible inhibitor of the ErbB family that is expected to inhibit tumors with activating EGFR mutations more strongly than are reversible EGFR-TKIs. Our preclinical study revealed that afatinib prolonged survival compared with gefitinib in an *egfr*-driven mouse lung cancer model [8]. In a clinical study, afatinib significantly improved outcomes in treatment-naïve patients with NSCLC harboring EGFR mutations compared with gefitinib [9]. In a combined analysis of phase III studies comparing afatinib with platinum-based chemotherapy, afatinib significantly prolonged both PFS and OS [10], while first-generation EGFR-TKIs (gefitinib or erlotinib) prolonged PFS but not OS [2,3]. Thus, second-generation EGFR-TKIs are suggested to achieve better outcomes than those of first-generation inhibitors.

Vascular endothelial growth factor (VEGF)-A, by binding to the VEGF receptor (VEGFR)-2, promotes angiogenesis in the tumor microenvironment and indirectly promotes tumor growth. We previously described the synergistic effects of afatinib and bevacizumab, a recombinant monoclonal antibody targeting VEGF-A [8]. In our preclinical study, the combination of bevacizumab with afatinib was more effective than afatinib alone in a xenograft model of NSCLC cells harboring EGFR mutations. Clinically, we and another group have already shown favorable PFS with acceptable toxicity profiles for combination therapy consisting of bevacizumab and first-generation EGFR-TKIs in untreated EGFR-mutant tumors [11–13]. The median PFSs of patients treated with erlotinib/bevacizumab therapy and gefitinib/bevacizumab therapy were 16.0 months and 14.4 months, respectively. However, combination therapy of bevacizumab with the second-generation EGFR-TKI afatinib had not been evaluated clinically.

Against this background, we hypothesized that the combination of bevacizumab with afatinib would yield improved efficacy. As the first step to test this hypothesis, we initiated a phase I trial of this combination therapy in chemo-naïve patients with advanced NSCLC harboring EGFR mutations.

2. Materials and methods

2.1. Study design

This open-label, phase I study was conducted in 16 institutions in Japan (UMIN000015944). The study protocol was approved by the institutional review boards of each participating center. Written informed consent was obtained from each patient prior to the study. This study was performed in accordance with the Declaration of Helsinki and all relevant Japanese laws and regulations.

The aim of this study was to evaluate the feasibility and recommended dose of combination therapy in chemo-naïve patients with advanced NSCLC harboring EGFR mutations. The primary outcome measure was dose-limiting toxicity (DLT). Secondary outcome measures were the objective response rate, PFS, OS, and specific toxicity.

2.2. Patients

Those patients who met the following criteria were eligible: histologically or cytologically confirmed stage IIIB/IV or postoperative recurrent non-squamous NSCLC with activating EGFR mutations (either exon 19 deletion or Leu858Arg), age ≥20 years, Eastern Cooperative Oncology Group performance status of 0 or 1, adequate organ function, and life expectancy of 3 months or more. Those who received previous EGFR-TKI therapy or radiation therapy for lung tumors were excluded. Tumor samples were screened by PCR-based hypersensitive EGFR mutation testing in local laboratories, according to standard testing practices.

Major exclusion criteria included confirmation of the Thr790Met mutation, presence of symptomatic brain metastasis or leptomeningeal carcinomatosis, history or presence of hemoptysis, bloody sputum or a coagulation disorder, tumor invading or abutting major blood vessels, tumor cavitation, or coexisting or previous interstitial lung disease.

2.3. Treatment regimen

Six patients were first scheduled to receive 40 mg afatinib daily plus 15 mg/kg intravenous bevacizumab repeated at 3-week intervals (level 0) until disease progression or unacceptable toxicity was observed. If no more than two patients experienced DLT, an additional six patients were treated at the same dose. If no more than two patients experienced DLT in both sets (a rate or DLT < 33.3%), we concluded this dose schedule to be feasible and planned a subsequent phase II trial. Otherwise, we repeated the same treatment of 30 mg/day afatinib and 15 mg/kg bevacizumab (level −1). If four or fewer patients experienced DLT (a rate of DLT < 33.3%), this level was recommended; if not, further investigation of this combination therapy was not pursued.

2.4. Safety and efficacy assessment

Severity of toxicity was assessed according to the Common Terminology Criteria for Adverse Events v 4.0. Although all treatment courses were analyzed to determine the DLT and maximum tolerated dose, the decision to lower the dose level was based on toxicity during the first 28 days from initiation of the combination therapy. A DLT was defined as any of the following adverse drug reactions: grade 4 hematological toxicity, grade 4 hypertension, grade 3 or worse non-hematological toxicity other than hypertension, grade 2 non-hematological toxicity lasting ≥7 days despite supportive care, grade 2 or worse left ventricular function or renal function, grade 1 or worse pneumonitis, or inability to receive the second course of bevacizumab due to bevacizumab toxicity.

Antitumor activity was assessed radiologically (by computed tomography or magnetic resonance imaging) every 2 months. All responses were defined according to the criteria of RECIST 1.1. If a patient had a documented complete response (CR) or partial response (PR), a confirmatory evaluation was performed after 4 weeks. Disease control was defined as the best tumor response among CR, PR, and stable disease (SD) that had been confirmed and sustained for at least 6 weeks. The response rate (RR) was defined as the number of patients with the best tumor response (CR or PR) among all patients with measurable lesions. OS was defined as the time from the date of registration to death from any cause. PFS was defined as the time from the date of registration to the date of the detection of progressive disease or of death from any cause. OS and PFS were assessed by the Kaplan-Meier method.

3. Results

3.1. Patient characteristics

From December 2014 to July 2016, 19 patients were enrolled, of whom 5 were treated at dose level 0 and 14 at dose level −1. The clinical characteristics of all patients are listed in Table 1. Three patients were withdrawn for toxicity (Fig. 1).