Rationale and Design of a Randomized Phase 2 Trial of Gefitinib Plus Bevacizumab vs Gefitinib Alone in Patients with Epidermal Growth Factor Receptor Mutant Non-Squamous Non-Small-Cell Lung Cancer: Study Protocol

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Summary: Combination chemotherapy with platinum preparations is the standard first-line treatment for stage IIIB/IV non-small-cell lung cancer. However, the median survival in patients receiving this therapy is 8 to 10 months, and it is essential to improve the results of chemotherapy in non-small-cell lung cancer. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors hinder EGFR signal transmission by binding to the adenosine triphosphate binding site of intracellular tyrosine kinase and inhibiting the autophosphorylation of EGFR. They are a standard initial treatment option in EGFR gene mutation-positive patients. In Japan, gefitinib is routinely used. A combination of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) and another antineoplastic drug may be a strategy to further improve treatment outcomes. We planned a randomized phase 2 trial to assess the efficacy and safety of gefitinib plus bevacizumab in such patients. In this study, subjects will be assigned to receive monotherapy with gefitinib (GEF group) or combination therapy with gefitinib and bevacizumab (GEF+BEV group) as the initial treatment at a ratio of 1:1. EGFR gene mutations are frequently detected in Asian patients with non-small-cell lung cancer. This study may be significant for establishing a new standard treatment.

Key words gefitinib, bevacizumab, epidermal growth factor receptor, non-small-cell lung cancer

INTRODUCTION

Combination chemotherapy with platinum preparations is the standard first-line treatment for stage IIIB/IV non-small-cell lung cancer, for which neither surgery nor radical radiotherapy is indicated. However, the median survival in patients receiving this therapy is 8 to 10 months, and it is essential to improve the results of chemotherapy in non-small-cell lung cancer. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs) hinder EGFR signal transmission by binding to the adenosine triphosphate binding site of intracellular tyrosine kinase and inhibiting the autophosphorylation of EGFR. Some clinical studies initially demonstrated the tumor-reducing effects of EGFR-TKIs after secondary treatment.

Abbreviations: BEV, bevacizumab; CBDCA, carboplatin; CDDP, cisplatin; CR, complete response; CT, computed tomography; EGFR, epidermal growth factor receptor; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; FAS, full analysis set; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PPS, per protocol set; PR, partial response; PTX, paclitaxel; RECIST, response evaluation criteria in solid tumors.
However, the true predictive factor for the efficacy of gefitinib was initially unclear, although patients with marked improvement were often reported. A phase III study involving subjects enrolled without patient selection did not show any significant survival benefit. In 2004, the presence of EGFR gene mutations in patients with non-small-cell lung cancer was reported, and several studies indicated that the presence or absence of EGFR gene mutations was associated with the effects of EGFR-TKIs [1-3]. Such mutations were detected at Exons 18-21 in the tyrosine kinase area: Exon 19 deletion accounted for 44%, L858R accounted for 41%, and other mutations (G719X or rare mutations) accounted for approximately 15% [4].

A phase III clinical study (Iressa pan Asia Study) was conducted to compare the efficacy of gefitinib with that of combination therapy with carboplatin (CBDCA) and paclitaxel (PTX), focusing on patients with clinical background factors (non-smokers, Asians, adenocarcinoma) for which EGFR-TKIs may be effective. The results showed that the progression-free survival (PFS) was significantly prolonged in the gefitinib group [5]. In the study, subanalysis with respect to the presence or absence of EGFR gene mutations was performed. Among patients with EGFR gene mutations, the PFS was significantly prolonged (hazard ratio (HR) =0.48, median PFS, gefitinib group: 9.5 months, CBDCA+PTX group: 6.3 months). However, among those without EGFR gene mutations, the PFS in the gefitinib group was unfavorable (HR=2.85, median PFS, gefitinib group: 1.5 months, CBDCA+PTX group: 5.5 months) despite clinical-background-based patient selection, suggesting that EGFR gene mutations are a predictive factor for efficacy. Thereafter, several phase III comparative studies of combination therapy with an EGFR-TKI and platinum preparation as the initial treatment, involving patients with EGFR gene mutations, were conducted. The results of all studies that have been published showed a significant prolongation of the PFS. Among these studies, a phase III study comparing gefitinib with CBDCA+PTX in Japan (NEJ002 study) [6] and another phase III study comparing gefitinib with cisplatin (CDDP) + docetaxel therapy (WJTOG3405 study) [7] indicated that the PFS was significantly prolonged in the gefitinib group (NEJ002: HR=0.30, median PFS, gefitinib group: 10.8 months, CBDCA+PTX group: 5.4 months, WJTOG3405: HR=0.52, median PFS, gefitinib group: 9.6 months, CDDP+DTX group: 6.6 months). However, in these studies, there was no significant difference in the overall survival (OS). This may have been related to an extremely high rate of crossover to EGFR-TKI at posttreatment in the platinum-combined groups. The median OS in the gefitinib and CBDCA+PTX groups in the NEJ002 study was 30.5 and 23.6 months, respectively, and that in the gefitinib and CDDP+DTX groups in the WJTOG3405 study was 35.5 and 38.8 months, respectively, being markedly more favorable than the previously reported results of clinical studies involving patients with stage III/IV non-small-cell lung cancer. Other phase III studies comparing erlotinib with platinum-combined therapy involving the same population (EURTAC [8] and OPTIMAL [9] studies) also showed similar results. According to these studies, in the platinum-combined therapy groups, the OS was shorter in patients in whom a crossover to EGFR-TKI was impossible; therefore an EGFR-TKI may be a key drug for patients with EGFR gene mutations. EGFR-TKIs should be used for first-/second-line treatment in patients in whom they are available in the absence of patient refusal. EGFR-TKI therapy is a standard initial treatment option for patients with EGFR gene mutations. In particular, gefitinib, which was first approved as initial treatment, is routinely used in Japan.

A combination therapy of EGFR-TKI and another antineoplastic drug may further improve treatment outcomes, which is the next objective. A preclinical trial with a mouse model showed that a combination of gefitinib+bevacizumab was effective for treating gefitinib-resistant EGFR gene mutation-positive lung cancer [10]. EGFR signaling in the tumor stroma is associated with bevacizumab resistance, and EGFR-TKI+bevacizumab combination favorably suppressed angiogenesis [11]. A foreign phase III clinical trial compared erlotinib monotherapy with an erlotinib + bevacizumab combination as a second-line therapy for patients with advanced non-small-cell lung cancer who were not selected by EGFR gene mutation [12]. Although overall survival, which is the primary endpoint, was not prolonged in that study (HR 0.97, p=0.758), the HR was 0.62 (p<0.0001) for the secondary PFS endpoint, with 12.3% and 6.2% response rates for combination and monotherapy cohorts, respectively (p=0.006). An EGFR gene-mutation positive subgroup was analyzed [13], and the median PFS was 17.1 months for the combination therapy and 9.7 months for the monotherapy (HR 0.52, p=0.828), suggesting that combination therapy may prolong PFS in patients with EGFR mutation-positive NSCLC, although the sample size was small. Furthermore, the same trial was conducted with a normal dose setting of bevacizumab (15 mg/kg) and erlotinib (150 mg) following the results of an earlier foreign phase I trial. There were no new toxicities besides the toxicity profile of each
drug, and the investigators reported that the toxicity was tolerable for both groups. According to existing reports, the toxicity profile of gefitinib is about the same that of erlotinib, although the incidence of rash or diarrhea is known to be generally lower with gefitinib than with erlotinib. Therefore, we planned this trial to evaluate the efficacy and safety of bevacizumab and gefitinib doses at normal dose settings.

**METHODS**

**Inclusion criteria**

1) Patients diagnosed with non-small-cell lung cancer other than squamous cell carcinoma based on the results of histo-/cytodiagnosis

2) Those evaluated as having an active EGFR gene mutation (Exon 19 deletion or L858R mutation) using a high-sensitivity EGFR gene mutation test

3) Stage III/IV (in accordance with the 7th version of TNM staging) patients or those with postoperative relapse for whom radical radiotherapy is not indicated

4) Those who have not received EGFR-TKI therapy or chemotherapy (However, postoperative adjuvant therapy with UFT or intrathoracic pretreatment with OK-432 is permissible, but the interval from the final administration of UFT or OK-432 until the start of this study should be ≥ 2 weeks.)

5) Those aged ≥ 20 years on the day of informed consent

6) Those with an Eastern Cooperative Oncology Group Performance Status score of 0-1

7) Those with measurable lesions (maximum diameter: ≥ 20 mm at a slice thickness of ≤10 mm on conventional computed tomography (CT), or ≥ 10 mm on helical CT with ≤ 5-mm continuous re-arrangement algorithms)

8) Those in whom the functions of the main organs (bone marrow, lungs, liver, kidneys, and heart) are maintained

9) Those with a life expectancy of ≥ 3 months

10) Those from whom written informed consent regarding participation in this study was obtained

**Exclusion criteria**

1) Patients with a history of interstitial lung disease, drug-induced interstitial disease, or radiation pneumonia requiring steroid therapy, or those with interstitial pneumonia or pulmonary fibrosis on thoracic CT

2) Those with an EGFR gene mutation (T790M) who were not expected to be susceptible to gefitinib

3) Those with brain metastasis

4) Those with spinal cord compression

5) Those with active double cancer

6) Those with a history of hemoptysis or bloody sputum or with these symptoms

7) Those with a bleeding tendency, such as coagulation disorder

8) Those receiving anticoagulants

9) Those with tumor infiltration in the thoracic great vessel on imaging

10) Those with cavitation of a pulmonary lesion on imaging

11) Those with superior vena cava syndrome

12) Those with celomic fluid (pleural effusion, ascites, pericardial fluid) requiring drainage (However, enrollment is possible if the interval from drainage/pleurodesis is ≥ 2 weeks. As an adhesive agent, only OK432 or Minomycin is permissible. The use of other anticancer drugs is not acceptable.)

13) Those with symptomatic cerebrovascular disorder or its history within 1 year

14) Those with perforation of the digestive tract or its history within 1 year

15) Those with diverticulitis

16) Those with serious complications (serious heart disease/cerebrovascular disorder, serious hypertension, active peptic ulcers, diabetes mellitus of which the control is difficult, or clinically significant psychiatric/neurological diseases)

17) Those with a history of drug allergy who are considered to be ineligible for participation in this study

18) Those with active infectious diseases that may affect this treatment

19) Those who received oral steroids or immunosuppressive drugs within 2 weeks before registration

20) Those who underwent surgery within 3 weeks before registration or pretreatment, such as radiotherapy, within 2 weeks

21) Pregnant women, lactating women, or those who may become pregnant

22) Patients involved in the planning and implementation of this study (employees/staff of partnership corporations or medical institutions participating in this study)

23) Others who are considered to be ineligible as subjects by the attending physician or principal investigator

**Test treatment**

Subjects will be assigned to receive monotherapy with gefitinib (GEF group) or combination therapy with gefitinib and bevacizumab (GEF+BEV group) as...
the initial treatment at a ratio of 1:1 by the minimization method using the sex (male/female) and clinical stage (stage IIIb, postoperative relapse/stage IV) as assignment-adjusting factors. In the two groups, each subject will take a 250-mg gefitinib tablet once a day. In the GEF+BEV group, bevacizumab at 15 mg/kg will be intravenously infused on Day 1 of each cycle consisting of 3 weeks (21 days). In the two groups, treatment will be continued if criteria for the discontinuation of treatment are not met.

Endpoints

PFS is a primary endpoint. We defined PFS as duration from registration to the earliest day of disease progression by CT/magnetic resonance imaging image evaluation based on response evaluation criteria in solid tumors (RECIST) ver.1.1 and death regardless of the cause. Surviving cases without disease progression are censored on the last day absence of progression was confirmed.

Secondary endpoints consist of the OS, antitumor effects (response rate, disease control rate), and incidence of adverse events. OS was defined as duration from registration to the death date due to any cause. Surviving patients will be censored at the final survival confirmation date. The response rate is defined as the proportion of patients with a complete response (CR) or partial response (PR) in the best overall effect by RECIST. The disease control rate is the proportion of patients that are either CR, PR or stable disease.

Sample size

Based on the results of previous clinical studies, the median PFS in GEF-treated subjects may be approximately 10 months [5-7]. Furthermore, a subset analysis of a small number of patients receiving combination therapy with bevacizumab and EGFR-TKIs showed that the median PFS was approximately 17 months [12, 13]. Assuming that the median PFS in the GEF and GEF+BEV groups may be 10 and 17 months, respectively, the required number of patients was calculated as 42 per group when assigning subjects to receive GEF or GEF+BEV at a ratio of 1:1 under the following conditions: one-sided significance level of 0.1, statistical power of 0.80, registration period: 24 months, and follow-up period: 18 months. Therefore, we established the total number of patients as 90 (GEF group: 45, GEF+BEV group: 45), considering drop-outs.

Statistical analysis

Of registered and assigned patients will be regarded as a full analysis set (FAS). An analysis set that does not have a serious protocol violation, and for which the efficacy can be evaluated, is defined as a per protocol set (PPS). Patients treated with the test drug at least once after the start of this study will be regarded as a population to be analyzed for drug safety.

For primary analysis with FAS, the survival function for PFS will be estimated using the Kaplan-Meier method, and the median PFS and confidence interval will be calculated. The results will be compared between the two groups using log-rank test. Furthermore, the hazard ratio of the PFS in the GEF+BEV group compared to that in the GEF group will be calculated using the Cox proportional hazard model involving assignment-adjusting factors, such as sex and clinical stage. Response rate, disease control rate, and their 95% confidence intervals will be calculated. The survival function of OS will be estimated using the Kaplan-Meier method.

The incidences of adverse events in the two groups will be calculated in the population to be analyzed for drug safety.

DISCUSSION

In this study, monotherapy with GEF and GEF+BEV combination therapy will be performed as the initial treatment for advanced non-small-cell lung cancer (non-squamous cell carcinoma) patients with EGFR gene mutations to compare their efficacy and safety. Gefitinib was approved for non-resectable or recurrent non-small-cell lung cancer patients with EGFR gene mutations. Its effects were more potent than those of conventional chemotherapy; gefitinib is routinely used as the standard initial treatment in Japan and other countries. EGFR gene mutations are frequently detected in Asian patients with non-small-cell lung cancer, accounting for approximately 30% of the total. It is important to conduct a clinical study involving these patients in Japan for the improvement of treatment. This study may be significant for establishing a new standard treatment.

DECLARATION

Competing interests

The authors declare that they have no conflict of interests.

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Authors’ contributions

CK, YI and HS conceived of the study, participated in its design and coordination, and developed the manuscript. AK participated in the design of the study and performed the statistical analysis. AMS assisted with drafting the protocols and conducting the quality control procedures (data management and monitoring). All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics committee of Nagoya Medical Center (No. 2014-737), and registered in UMIN-CTR on April 1, 2014 (UMIN 000013586). Written informed consent will be obtained from every patient participating in the study.

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