Erlotinib and bevacizumab in elderly patients ?75 years old with non-small cell lung cancer harboring epidermal growth factor receptor mutations

Erlotinib and bevacizumab in elderly patients ≥75 years old with non-small cell lung cancer harboring epidermal growth factor receptor mutations

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Abstract

Purpose: The efficacy and safety of combination therapy with erlotinib and bevacizumab in elderly patients with non-small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor (*EGFR*) gene mutations are unknown.

Methods: Elderly patients aged ≥75 years old with advanced or recurrent NSCLC and *EGFR* mutations (exon 19 deletion or L858R mutation in exon 21) received erlotinib (150 mg, daily) and bevacizumab (15 mg/kg on day 1 of a 21-day cycle) until disease progression or the occurrence of unacceptable toxicities. The primary endpoint was progression-free survival from enrollment.

Results: Twenty-five patients were enrolled in this study, and the median age was 80 years. Fifteen (60.0%) and 10 patients (40.0%) had exon 21 L858R mutations and exon 19 deletions, respectively. The median progression-free survival from enrollment was 12.6 months [95% confidence interval (CI): 8.0–33.7 months]. The objective response rate was 88.0% [95% CI: 74.0%–99.0%], and the disease control rate was 100% [95 % CI: 88.7%–100%]. Grade 3 or higher adverse events occurred in 12 patients (48.0%), and rash and nausea were the most common. Grade 3 or higher bevacizumab-related toxicities occurred in 4 (16.0%) patients, including proteinuria (n=2), gastrointestinal perforation (n=1) and pneumothorax (n=1). A dose reduction of erlotinib and cessation of bevacizumab was required in 16 (64.0%) and 18 patients (72.0%), respectively.

Conclusion: Erlotinib and bevacizumab combination therapy showed a minimal survival

benefit with frequent dose reductions and/or treatment discontinuations in elderly patients with *EGFR*-positive NSCLC.

Keywords: bevacizumab, elderly patients, epidermal growth factor receptor mutation, erlotinib, targeted therapy.

Introduction

Epidermal growth factor receptor (*EGFR*) mutations are a major target for the treatment of non-small-cell lung cancer (NSCLC) [1]. In patients with *EGFR* mutation-positive NSCLC, EGFR tyrosine kinase inhibitors (EGFR-TKIs) have shown significant survival benefits compared with conventional platinum-based therapy and are currently used as standard therapy [2,3]. The first-generation EGFR-TKI erlotinib has been shown to prolong progression-free survival (PFS) compared with chemotherapy in phase III trials and is considered a first-line treatment option for *EGFR* mutation-positive NSCLC [3-5].

Elderly patients account for a major proportion of NSCLC patients in clinical practice. Because they have impaired organ function and several co-morbidities, they do not always experience clinical benefits from standard treatments that apply to the general population [6,7]. Unlike conventional chemotherapies, EGFR-TKIs are relatively less toxic, especially in terms of hematologic toxicities [3,4], and thus are suitable for elderly patients. We previously evaluated the efficacy and safety of erlotinib in patients with *EGFR*-positive NCSLC aged >75 years in a phase II study. Single erlotinib treatment achieved a median PFS of 15.5 months, which was comparable with those in the general population and was also well-tolerated [8].

Bevacizumab, a monoclonal anti-vascular endothelial growth factor (VEGF) antibody, enhances the effects of anti-cancer agents by altering the physiology of tumor blood vessels and increasing the uptake of drugs into tumors [9-12]. Bevacizumab has

shown therapeutic benefits in combination with several anti-cancer agents, such as platinum-based therapy [13,14]. When combined with erlotinib, bevacizumab has shown therapeutic benefits compared with erlotinib alone [15,16]. As a result, combination therapy with erlotinib and bevacizumab is now a treatment option for *EGFR*-positive NSCLC [5].

However, the clinical benefits of adding bevacizumab to erlotinib in elderly patients are still unknown. We conducted a phase 2 study to evaluate the efficacy and safety of erlotinib and bevacizumab in elderly patients ≥75 years old with NSCLC harboring activating *EGFR* mutations.

Patients and methods

Study design

This study was a single-arm, open-label, multicenter, phase II trial. This study was performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of each participating institution. Informed consent was obtained from all individual participants included in the study. The trial was registered with the University Hospital Medical Information Network Clinical Trial Registry (ID: 000016904).

Patient eligibility

The eligibility criteria were as follows: chemotherapy-naïve patients with pathologically confirmed non-squamous NSCLC with active *EGFR* mutations (exon 19 deletion or exon 21 L858R); stage IIIB without indication of definitive radiotherapy, stage IV or recurrent disease; over 75 years old; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; and adequate renal, hepatic and hematopoietic function. Palliative radiation therapy was allowed ≥2 weeks before enrollment unless the primary tumor site was irradiated. Exclusion criteria included severe uncontrolled complications, active interstitial lung disease, a history of hemoptysis, uncontrolled brain metastasis, uncontrolled body fluid retention, blood coagulation disorders and active metachronous cancer. Patients with *EGFR* mutations other than exon 19 deletions or L858R were also excluded.

Treatment schedule

Patients received erlotinib (150 mg, daily) and bevacizumab (15 mg/kg on day 1 of a 21-day cycle). The treatment was continued until disease progression or the development of unacceptable toxicity. The dose of erlotinib was reduced to 100 mg and then 50 mg based on the occurrence and severity of hematologic or non-hematologic toxicities. Treatment delays within 3 weeks were also permitted. When a dose reduction of more than the permitted range or a delay of >3 weeks was required, patients were withdrawn from the study. As for bevacizumab, treatment was discontinued in patients who had intolerable

toxicity. The evaluation of treatment responses was repeated every two cycles according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [17]. Adverse events were graded using the Common Terminology Criteria for Adverse Events version 4.0.

Statistical analyses

The primary endpoint was PFS from the enrollment of the study. Secondary endpoints were the overall response rate (ORR), disease control rate (DCR), overall survival (OS) from the enrollment of the study and safety. Based on the SWOG one-arm survival design, a total of 23 patients were required to achieve 80% statistical power with an α error of 0.05 and β error of 0.20, assuming an expected PFS of 16 months and threshold PFS of 9.7 months [16]. The planned cohort size was 25 patients after accounting for a 10% dropout rate. The Kaplan–Meier method was used to analyze PFS and OS. The log-rank test was used to compare the differences between the two groups. Hazard ratio (HR) was estimated using Cox regression analysis. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.0.2) [18].

Results

Between May 2015 and July 2018, 25 patients were enrolled in this study (Figure 1). Patient characteristics are shown in Table 1. The median age was 80 years (range: 75–89 years), and 18 patients (72.0%) were female. Sixteen patients (64.0%) had an ECOG performance status of 0, and 21 (84.0%) had stage IV disease. All patients had histologic diagnoses of adenocarcinoma, and 15 (60.0%) and 10 (40.0%) patients had *EGFR* exon 21 L858R mutations and exon 19 deletions, respectively. At the time of enrollment, six patients had previously treated stable brain metastases. Thirteen (52.0%), five (20.0%) and three patients (12.0%) had hypertension, diabetes and cardiovascular disease, respectively. The median follow-up time was 19.7 months (range: 0.9–43.3 months).

The median PFS from enrollment was 12.6 months (95% confidence interval [CI]: 8.0–33.7 months; Figure 2). As for mutation subtype, patients with an exon 19 deletion had a tendency of longer PFS compared with those with an L858R mutation (median PFS of 33.7 months [95%CI, 3.8 months – not reached] and 12.6 months [95%CI, 8.0–23.3 months], respectively), but there was no significant difference (hazard ratio: 0.83, 95% CI: 0.30–2.29, log-rank $p = 0.71$). The median OS from enrollment was not reached (95% CI: 34.0 months– not reached; Figure 3). Twenty-two patients (88.0%) showed a partial response (PR), and three (12.0%) showed stable disease (SD), yielding an ORR of 88.0% (95% CI: 74.0%–99.0%; Figure 4) and DCR of 100% (95 % CI: 88.7%–100%).

The major adverse events are listed in Table 2. The most common toxicities of

any grade were rash, nausea, nail disorder and diarrhea. Grade 3 or higher toxicities were observed in 12 patients (48.0%), and rash and nausea were the most common (both occurred in 4 patients). Pneumonitis was observed in two patients (8.0%) but was mild (grade 1). The most common bevacizumab-related toxicities were proteinuria (n=7, 28.0%), bleeding (n=6, 24.0%) and hypertension (n=4, 16.0%). Grade 3 or higher bevacizumab-related toxicities were observed in four patients (16.0%), including proteinuria (n=2, 8.0%), gastrointestinal perforation (n=1, 4.0%) and pneumothorax (n=1, 4.0%).

A median of 7 cycles (range: 1–41 cycles) and 4.5 months (range: 0.7–43.3 months) of bevacizumab therapy were administered. Except for disease progression, 18 patients discontinued bevacizumab therapy based on severe and non-severe adverse events and their decision (Table 2). For erlotinib, the median treatment duration (with or without bevacizumab) was 10.4 months (range: 0.9–43.3 months). The dose of erlotinib was reduced in 16 (64.0%) patients (14: 100 mg and 2: 50 mg). The most common reasons for the reduction was rash (n=9, 36.0%), nausea (n=4, 16.0%) and nail disorders (n=2, 8.0%). Four patients were still receiving the study therapy at the data collection cutoff (1: erlotinib and bevacizumab and 3: erlotinib alone).

Among the 21 patients who discontinued the study therapy, 10 (40.0%) received second-line treatments including four gefitinib, three osimertinib, two platinum-based chemotherapies and one single agent chemotherapy.

Discussion

In the current study, we evaluated the efficacy and safety of erlotinib and bevacizumab in elderly patients with *EGFR* mutation-positive NSCLC. The median PFS of 12.6 months exceeded the preplanned lower threshold level of 9.7 months; however, it did not reach the expected level of 16.0 months. Although the ORR of 88.0% was favorable, the discontinuation of treatment was frequent, which may result in limited survival benefit of adding bevacizumab to erlotinib in elderly patients.

The addition of bevacizumab enhanced the short-term efficacy of erlotinib in elderly patients. The ORR of 88.0% and DCR of 100% in the current study were numerically superior to those in our previous study that evaluated single erlotinib treatment in elderly patients (56% and 90%, respectively) [8]. Our results were also similar to a phase III study that evaluated the efficacy of erlotinib and bevacizumab in patients of all age groups (ORR of 72% and DCR of 95%) [19]. Bevacizumab is considered to enhance the effect of chemotherapeutic agents by normalizing blood flow in tumor blood vessels, improving drug delivery and restoring resistance to the VEGF mediated pathway [20,21]. Additionally, an increase in VEGF via hepatocyte growth factor (*HGF*) expression plays an important role in drug resistance to EGFR-TKIs [22].

In contrast to response rates, the median PFS of 12.6 months was numerically shorter than that observed in the study of erlotinib and bevacizumab in all ages (16.9

months), and it was even shorter than those reported in a study of single erlotinib treatment in all ages (13.1 months) and elderly patients (15.5 months) [3,8,19]. In this study, about 72% of the study patients discontinued combination therapy because of reasons other than disease progression. As a result, the median duration of erlotinib and bevacizumab combination therapy was 136 days, which was substantially shorter than the 350 days reported for the identical treatment in all ages [19]. The short treatment duration in elderly patients may reduce the long-term efficacy. In a subgroup analysis of the SAiL study, the median treatment duration was 17.3 weeks in elderly patients ≥65 years old, which was numerically shorter than the 22.4 weeks in patients < 65 years old [23].

The impact of age on the occurrence of bevacizumab-related toxicities is controversial. In the ECOG 4599 trial that examined the outcomes of bevacizumab in combination with carboplatin and paclitaxel, adding bevacizumab resulted in more occurrences of severe toxicities in elderly patients [24]. Laskin et al. reported in an international phase IV trial that NSCLC patients ≥65 years old who received bevacizumab in combination with cytotoxic chemotherapy did not experience increased toxicities, compared with those < 65 years old [23]. The occurrence of grade 3 or higher toxicities in the current study was 48%, which was less than that for the identical treatment with erlotinib and bevacizumab in the all age population (88%) [19]. In the current study, age was not a risk for the occurrence of severe toxicities.

Among 13 patients who experienced mild (grade 2 or lower) toxicities in this

study, seven patients discontinued the study therapy (Table 2). Although the percentage of patients who experienced bleeding of any grade was 24%, which was equivalent to that in the all age group [19], and no patient experienced severe bleeding, three patients discontinued bevacizumab. In an observational study of patients who received first-line treatment with bevacizumab and platinum-based chemotherapy, more patients ≥75 years discontinued treatment than those < 75 years, even though the occurrence of adverse events was comparable between the two groups [25]. In elderly patients, the impact of adverse events on their quality of life and/or motivation for treatment might be relatively more significant than in the younger population, resulting in the attending physicians or patients choosing to discontinue the study treatment even if non-severe toxicity occurred.

This study had two main limitations. First, the optimal dose of erlotinib for elderly patients, especially when combined with bevacizumab, was unknown. In fact, 64% of the patients required a dose reduction of erlotinib, which was higher than the 56% observed in the previous study of single erlotinib in elderly patients [8]. Bevacizumab has the potential to enhance both the toxicity and efficacy of a combination agent [19]. When combined with bevacizumab, a lower dose of erlotinib would be feasible for elderly patients. Second, new treatment options for *EGFR*-positive NSCLC have recently emerged, such as osimertinib, chemotherapy plus gefitinib, or erlotinib plus ramucirumab [26-30]. The clinical benefits of these new treatments for elderly patients are still unknown. Therefore, further studies are needed to elucidate the optimal treatment for

elderly patients with *EGFR*-positive NSCLC.

Conclusions

In elderly patients with *EGFR*-positive NSCLC, combination therapy with erlotinib and bevacizumab showed favorable ORRs but required frequent dose reduction and/or treatment discontinuation and resulted in no survival benefit.

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest

All authors declare no actual or potential conflicts of interest.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or

comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Table 1. Patient characteristics

	All patients, n=25
Age, years	80 (75–89)
Sex, female	18 (72.0)
Smoking status	
Never smoker	17 (68.0)
Former smoker	8 (32.0)
Current smoker	0
ECOG performance status	
0	16 (64.0)
1	9 (34.0)
Histology, adenocarcinoma	25 (100)
Stage	
IIIB	2 (8.0)
IV	21 (84.0)
relapse	2 (8.0)
EGFR mutation	
Exon 19 deletion	10 (40.0)
Exon 21 L858R	15 (60.0)
Charlson co-morbidity index	
No co-morbidity	13 (52.0)
1	9 (36.0)
2	1 (4.0)
≥3	2 (8.0)

Data are expressed as numbers (percentage) or median (range). ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor.

Table 2. Adverse events

	Grade 1-4	Grade 3-4	Event*
Anemia	3 (12.0)	0	1 (4.0)
Creatinine increase	3 (12.0)	0	0
ALT /AST increased	5 (20.0)	0	0
Rash	19 (76.0)	4 (16.0)	2 (8.0)
Nail disorder	9 (36.0)	0	0
Stomatitis	5 (19.2)	0	0
Nausea	10 (40.0)	4 (16.0)	4 (16.0)
Diarrhea	8 (32.0)	0	2 (8.0)
Taste disorder	4 (15.3)	0	0
Fever	2 (8.0)	0	1 (4.0)
Fatigue	3 (12.0)	0	0
Proteinuria	7 (28.0)	2 (8.0)	1 (4.0)
Hypertension	4 (16.0)	0	0
Intracranial hemorrhage	1 (4.0)	0	1 (4.0)
Nose bleeding	1 (4.0)	0	0
Upper gastrointestinal bleeding	2 (8.0)	0	1 (4.0)
Lower gastrointestinal bleeding	3 (12.0)	0	1 (4.0)
Gastrointestinal perforation	1 (4.0)	1 (4.0)	1 (4.0)
Pneumonitis	2 (8.0)	0	2 (8.0)
Pneumothorax	1 (4.0)	1 (4.0)	1 (4.0)
Febrile neutropenia	0	0	0

*Event related to drug discontinuation

Data are expressed as numbers (percentage). ALT, alanine aminotransferase; AST, aspartate aminotransferase

Figure legends

Fig 1. Study profile.

Fig 2. Progression-free survival.

The median progression-free survival measured from study enrollment was 12.6 months (95 % CI, 8.0–33.7 months).

Fig 3. Overall survival.

The median progression-free survival measured from study enrollment was not reached (95 % CI, 34.0 months –not reached).

Fig 4. Waterfall plots of percent changes from baseline in tumor diameters.

Best percent changes in target lesion size from baseline. Responders were confirmed by the Response Evaluation Criteria in Solid Tumors guidelines. PR=partial response. SD=stable disease.