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ORIGINAL ARTICLE

A phase II trial of induction of erlotinib followed by cytotoxic chemotherapy for *EGFR* mutation-positive non-squamous non-small cell lung cancer patients

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Abstract

Background No consensus has been reached regarding the treatment order and timing of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) and cytotoxic chemotherapy administration for EGFR mutation-positive non-small cell lung cancer (NSCLC) patients.

Methods In this phase II trial, chemotherapy-naïve patients harboring activating EGFR mutations with stage IIIB/IV or post-surgical recurrent non-squamous NSCLC were enrolled. Patients were treated with erlotinib induction at 150 mg/day for 3 months. This was followed by cytotoxic chemotherapy with platinum plus pemetrexed, with or without bevacizumab, when the induction erlotinib achieved a CR or PR. The primary end point was the 1-year progression-free survival (PFS) rate, while the secondary end points were the response rate (RR), PFS, safety, and overall survival (OS).

Results Twenty patients were enrolled in this study. The median age was 63 years. Eighteen patients had stage IV disease, and 2 patients had recurrent disease. Eleven patients achieved a PR after induction of erlotinib and 9 out of 11 patients were switched to chemotherapy. The 1-year PFS rate was 45.0% (90% CI 26.8–63.2), the overall RR was 55.0%, and the median PFS was 10.7 months in the intention-to-treat (ITT) population. Grade 3–4 adverse events were reported for 40% of the patients, including patients with leukopenia (10%), neutropenia (20%), and interstitial pneumonitis, bacterial pneumonia, rash, and nausea (all 5%).

Conclusions The primary end point of this study was not achieved. However, the therapy was well tolerated and may be a treatment option for a future study with patients responsive to short-term erlotinib treatment.

Clinical trials registration number UMIN ID: 000013125.

Keywords EGFR mutation · Erlotinib · Pemetrexed · Bevacizumab

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide [1]. Recent molecular characterizations of lung cancer have enabled us to identify driver oncogenes, such as EGFR, KRAS, and EML4-ALK rearrangement in non-small cell lung cancer (NSCLC) [2–6], especially non-squamous NSCLC. The frequency of EGFR mutations in the driver oncogene was among the highest in non-squamous NSCLC patients [7, 8]. In general, EGFR-TKI and platinum-based chemotherapy are effective for EGFR mutation-positive NSCLC patients. Platinum-based chemotherapy, the combination therapy of platinum and pemetrexed was one of the most effective therapies for these patients [9]. In the subgroup analysis of this trial, overall survival (OS) was

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statistically superior for cisplatin plus pemetrexed compared to cisplatin plus gemcitabine in NSCLC patients. In other clinical trials, the addition of bevacizumab to platinum-based chemotherapy was effective for non-squamous NSCLC patients [10, 11].

On the other hand, EGFR-TKIs, such as erlotinib, gefitinib, and afatinib, which target EGFR mutations, have excellent efficacy for EGFR mutation-positive NSCLC patients. Many clinical trials have been performed for EGFR mutation-positive NSCLC patients [12–19]. However, these results were inconclusive because almost all of the EGFR mutation-positive NSCLC patients did not achieve a complete response and finally acquired resistance to EGFR-TKI after approximately 1 year. To overcome these problems, several combination therapies of EGFR-TKI and other drugs or chemotherapeutic agents have recently been investigated [20, 21]. An interrelated combination therapy of platinum-based chemotherapy and erlotinib prolonged both PFS and OS compared to chemotherapy plus a placebo [20]. In a subgroup analysis of EGFR mutation-positive patients, combination therapy was more effective than chemotherapy alone; in this case, OS was 31.4 months with chemotherapy plus erlotinib, and 20.6 months with chemotherapy plus a placebo (hazard ratio [HR] 0.48 95% confidence interval [CI] 0.27–0.84; $p = 0.0092$). Another phase II trial showed that concurrent therapy was better than a sequential alternating therapy with gefitinib and carboplatin/pemetrexed [21]. It should be noted that in the other trial, PFS after administration of platinum-doublet chemotherapy during the initial response to gefitinib was 19.2 months [22]. On the other hand, erlotinib plus bevacizumab also prolonged PFS in EGFR mutation-positive NSCLC patients compared with erlotinib, for which PFS was 16.0 months with erlotinib plus bevacizumab, and 9.7 months with erlotinib alone (HR 0.54, 95% CI 0.36–0.79; $p = 0.0015$) [23]. However, these therapies could not cure lung cancer. We speculated that effective cytotoxic chemotherapy after short-term EGFR-TKI exposure with erlotinib for EGFR mutation-positive patients may eradicate the remaining cancer cells, which are resistant to EGFR-TKI, and cure patients in a certain population. We performed a phase II trial of induction of erlotinib followed by chemotherapy with platinum plus pemetrexed with or without bevacizumab for EGFR mutation-positive non-squamous NSCLC patients. This study was registered at UMIN-CTR under the study ID UMIN 000013125.

Patients and methods

Patient eligibility

Eligible patients were histologically or cytologically diagnosed with stage III/IV or post-surgically recurrent non-squamous chemotherapy-naïve NSCLC, with at least one measurable lesion (according to RECIST; Response Evaluation Criteria in Solid Tumors version 1.1). They also had an activating EGFR mutation (exon 19 deletion, Leu858Arg, Gly719X, or Leu861Gln) according to PCR-based hypersensitive EGFR mutation testing. Other criteria included Eastern Cooperative Oncology Group performance status 0–2 (before erlotinib) or 0–1 (before cytotoxic chemotherapy), age between 20 and 80 years, adequate hematological, hepatic, and renal functions, and a life expectancy of 3 months or more at the start of this trial. Exclusion criteria included the presence of active infection or interstitial lung disease, and severe complications. This study was approved by the institutional review board at Keio University School of Medicine. All patients provided written informed consent before this study.

Study design and treatment

The primary end point was the 1-year PFS rate, and the secondary end points were RR, PFS, adverse events, and OS. The study protocol is summarized in Fig. 1. Patients received induction of erlotinib orally once daily at a dose of 150 mg/day for 3 months, followed by four cycles of cytotoxic chemotherapy with platinum [75 mg/m^2 intravenous cisplatin or intravenous carboplatin with a target area under the curve (AUC) of 5, on day 1] plus pemetrexed (500 mg/m^2, intravenously, on day 1) with or without bevacizumab (15 mg/kg, intravenously, on day 1) every 3 weeks, when the

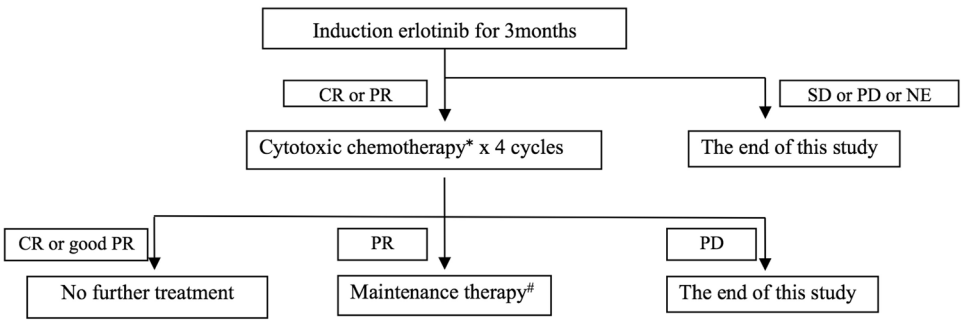

Fig. 1 A schematic view of the study protocol. *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *good PR* no FDG uptake in remaining tumors using FDG-PET. *Platinum (cisplatin or carboplatin) plus pemetrexed ± bevacizumab every 3 weeks; #pemetrexed ± bevacizumab every 3 weeks until PD

induction of erlotinib achieved a CR or PR. After four cycles of cytotoxic chemotherapy, if a CR or good PR [no fludeoxyglucose (FDG) uptake in the remaining tumors according to FDG-PET] were achieved, the patients received no further treatment. In the case of a PR, the patients received maintenance therapy with pemetrexed (500 mg/m^2, intravenously, on day 1 of a 3-week cycle) with or without bevacizumab (15 mg/kg, intravenously, on day 1 of a 3-week cycle). Bevacizumab was administered according to the judgment of an attending physician. However, patients with a history or presence of hemoptysis, coagulation disease, or a tumor that had invaded major blood vessels were excluded. Patients received treatment until disease progression or unacceptable toxicity developed. Dose reductions of erlotinib, cisplatin, carboplatin, and pemetrexed were permitted in the case of adverse events. Four dose reductions of erlotinib were permitted (100 mg/day, 50 mg/day, 25 mg/day, and 25 mg/every other day). The dose of cytotoxic agents could be reduced twice; cisplatin to 60 mg/m^2 or 50 mg/m^2, carboplatin to 4 or 3 AUC, and pemetrexed to 400 mg/m^2 or 320 mg/m^2.

Evaluation

Tumor response was evaluated using computed tomography, magnetic resonance imaging, and bone scintigraphy according to the RECIST criteria every 6 weeks until treatment cessation. FDG-PET was performed both after 3 months of erlotinib treatment and after four cycles of cytotoxic chemotherapy. During this study, physical examination, blood examinations, and chest radiography were performed at least once every 3 weeks. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for adverse events v. 4.0. The 1-year PFS rate, PFS, and OS were estimated using the Kaplan–Meier method.

Statistical considerations

The estimated minimum sample size was 19 with an α error of 0.05 (one-sided) and a β error of 0.2. The threshold 1-year PFS rate was 35% and the estimated 1-year PFS rate was 65%. We decided to enroll 20 patients into the study.

Results

Between April 2010 and February 2014, 20 patients were enrolled in this study. Table 1 shows the patients' characteristics. The median patient age was 63 years (range 40–78 years). The ECOG PS before erlotinib administration was 0 for 13 patients, 1 for 6 patients, and 2 for 1 patient. Histological analysis revealed that all patients had adenocarcinoma. The type of EGFR mutation was exon 19 deletion for 16 patients, Leu858Arg mutation for 2 patients, and Leu861Gln mutation for 2 patients. Eighteen patients had stage IV disease, and 2 patients had recurrent disease. Three patients had brain metastases. No patients had been previously treated with either cytotoxic chemotherapy or EGFR-TKI.

Table 1 Patient characteristics

	No. of patients
Total enrolled	20
Age (years)	
Median (range)	63 (40–78)
Sex	
Male	9
Female	11
Smoking	
Never	9
Current and former	11
ECOG performance status (pre-treatment)	
0	13
1	6
2	1
Histology	
Adenocarcinoma	20
Stage	
IIIB	0
IV	18
Recurrent	2
EGFR mutation	
Exon 19 deletion	15
Leu858Arg mutation	3
Leu861Gln mutation	2
Brain metastasis	
Positive	3
Negative	17

Efficacy

Table 2 shows the summarized efficacy results of this study. Among 20 patients, no patient achieved a CR, 11 patients had a PR, 5 patients had SD, 3 patients had PD, and 1 patient was not evaluable. Among the 11 patients who had PR, 9 patients were shifted to cytotoxic chemotherapy. Two patients received cisplatin + pemetrexed, five received cisplatin + pemetrexed + bevacizumab, and two received carboplatin + pemetrexed + bevacizumab. One patient did not receive chemotherapy because of interstitial pneumonia, and the other patient chose not to receive chemotherapy. Regarding the types of EGFR mutation status, of the 15 patients with an exon 19 deletion, 9 achieved a PR, 3 had SD, 2 had PD, and 1 was not evaluated. Of the three patients with a Leu858Arg mutation, two achieved a PR and one had

Table 2 Responses to the treatments

	No. of patients
Response of erlotinib	
Complete response	0
Partial response	11
Stable disease	5
Progression disease	3
Not evaluated	1
The enrollment of cytotoxic chemotherapy	9
Response of cytotoxic chemotherapy	
Complete response	0
Partial response	0
Stable disease	7
Progression of disease	2
Not evaluated	0
The enrollment of continuation therapy	7
Median cycle of continuation therapy (cycle)	9

SD, while of the two patients with a Leu861Gln mutation, one had SD and one had PD. Among the nine patients who received chemotherapy, seven received continued maintenance therapy.

The 1-year PFS rate was 45.0% (90% CI 26.8–63.2), and the median PFS was 10.7 months (95% CI 6.2–15.0) in the intention-to-treat population (Fig. 2a). The overall RR was 55.0% (90% CI 36.7–73.2). The median OS was 53.3 months (95% CI 16.9–not estimable) in the intention-to-treat population (Fig. 2b). Among the nine patients who had PR with erlotinib and were switched to receive cytotoxic chemotherapy, seven received rechallenge treatment with erlotinib after showing PD with chemotherapy. The median PFS in those patients was 11.9 months (95% CI not estimable–22.3) (Fig. 3).

Toxicity

Table 3 shows the grade 1 and 2 adverse events, which were reported by 10% of all patients, and all grade 3 and 4 adverse events in this study. The most commonly reported adverse events of any grade were rash, neutropenia, nausea, and liver dysfunction. Grade 3–4 adverse events were reported in 40% of the patients, including neutropenia (20%), leukopenia (10%), interstitial pneumonitis, bacterial pneumonia, rash, and nausea (all 5%). In general, rash and liver dysfunction occurred during erlotinib therapy, and hematological toxicities and nausea occurred during chemotherapy. One case of interstitial pneumonitis occurred during erlotinib therapy. Overall, most of the adverse events were well tolerated.

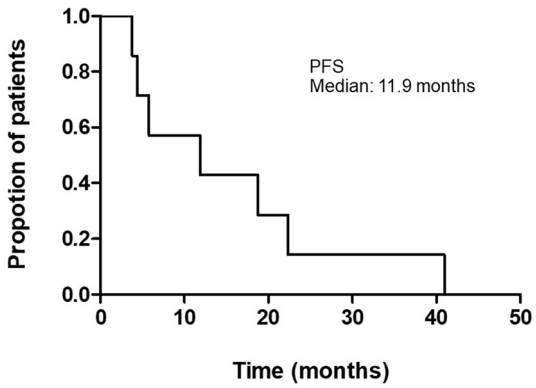

Fig. 3 Kaplan–Meier analysis of progression-free survival in the patients retreated with erlotinib ($n=7$)

Discussion

In this study, we investigated the efficacy and safety of the induction of erlotinib followed by chemotherapy with platinum plus pemetrexed, with or without bevacizumab, for EGFR mutation-positive non-squamous NSCLC patients. The primary end point of this study was not achieved; the 1-year PFS rate was 45.0%, and the median PFS was 10.7 months in the ITT population. The overall RR was 55.0% and no patient achieved a CR. Our initial speculation that the treatment in this study might be able to cure some of the lung cancer patients was also not realized. On the other hand, the toxicity of the therapies was well tolerated, and the frequency of adverse events was comparable to that of

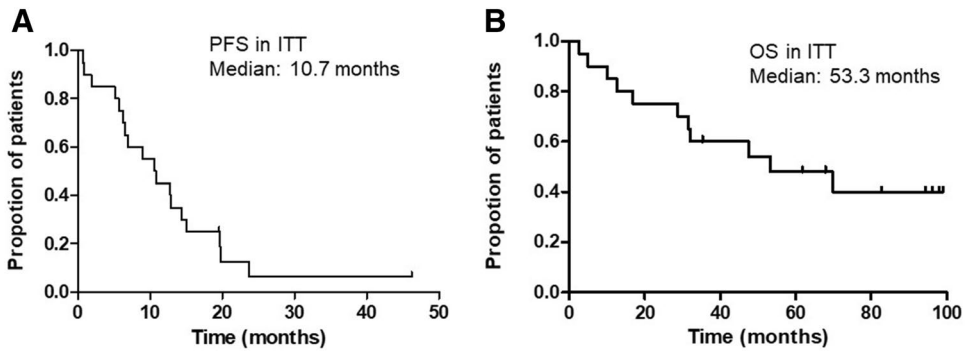

Fig. 2 Kaplan–Meier analysis for progression-free survival (PFS) and overall survival (OS). PFS (**a**) and OS (**b**) in ITT populations ($n=20$)

Table 3 Adverse events

	All grade (%)	Grade 3	Grade 4
Rash	14 (70)	–	–
Neutropenia	6 (30)	2	2
Nausea	4 (20)	1	–
Liver dysfunction	9 (45)	2	1
Leukopenia	5 (25)	1	1
Interstitial pneumonitis	1 (5)	1	–
Bacterial pneumonia	1 (5)	1	–
Anemia	5 (25)	–	–
Diarrhea	2 (10)	–	–
Paronychia	1 (5)	–	–
Thrombocytopenia	3 (15)	–	–
Proteinuria	2 (10)	–	–
Peripheral neuropathy	1 (5)	–	–
Stomatitis	6 (30)	–	–
Constipation	2 (10)	–	–
Anorexia	3 (15)	–	–
Dysgeusia	2 (10)	–	–
Nosebleed	1 (5)	–	–
Thrill	1 (5)	–	–
Hyponatremia	1 (5)	–	–
Renal dysfunction	4 (20)	–	–
Ear noises	1 (5)	–	–
Subcutaneous bleeding	1 (5)	–	–

previous reports. Two patients withdrew because of adverse events. One adverse event was interstitial pneumonitis and the other was bacterial pneumonia.

One of the reasons for the failure of this study was an unexpectedly low RR to erlotinib. In previous reports, the RRs of EGFR-TKI for EGFR mutation-positive patients were 70–80% [12–16], while the RR of this study was only 55.0%. Two patients with a minor mutation, namely L861Q, were included and they only developed either SD or PD with erlotinib. Moreover, even in patients with sensitive mutations, such as Del19 and L858R, the ORR was only 61% (11/18), with no clear explanation. On the other hand, the median PFS of 10.7 months in the ITT population in this study may be realistic, as it was reported to be 6.9 months in the subgroup of patients harboring EGFR mutations who were treated with cisplatin and pemetrexed in a former trial [17]. As none of the patients achieved a CR with erlotinib, all of them had residual tumors when they started to receive chemotherapy. As a consequence, even the responders to erlotinib could only achieve three additional months of PFS with erlotinib compared to the predicted PFS with chemotherapy. It is now obvious that the strategy in this study was not enough to cure the patients with EGFR mutations. However, surprisingly, the median PFS of the patients retreated with erlotinib after failure of chemotherapy was 11.8 months in patients who responded to first-line erlotinib. This extremely long PFS obtained using rechallenge with erlotinib might be due to the effective elimination of minor EGFR-TKI-resistant clones using cytotoxic chemotherapy. The median PFS for EGFR-TKI retreatment was reported to be 1.5–6.5 months in retrospective and prospective phase II studies [23–27]. In those studies and in practice, chemotherapy is administered after apparent resistance to EGFR-TKIs. In such situations, as the regrowing tumors contain a large number of TKI-resistant clones, chemotherapy may not be sufficient to kill all of these clones. In this protocol, chemotherapy was added before a large number of resistant clones could develop, which might be sufficient to eliminate a small number of residual resistant clones and contribute to prolonging PFS after the re-administration of erlotinib. This may also explain why concurrent or alternative treatments with EGFR-TKI and chemotherapy have demonstrated significant efficacy in previous reports [20, 21]. Osimertinib, a third-generation EGFR-TKI, showed significant efficacy and safety for NSCLC patients harboring EGFR-activating mutations and osimertinib has been already approved for untreated NSCLC patients with EGFR mutations [28]. However, osimertinib alone cannot cure lung cancer as first- or second-generation EGFR-TKIs could not. Immune checkpoint inhibitors targeting programed death 1 and programed death ligand 1 have shown great activity in the management of advanced NSCLC patients and cured the disease in some of them; however, unfortunately the benefit of this new treatment has been reported to be very limited on EGFR mutation-positive patients. In conclusion, the induction of erlotinib followed by chemotherapy may be a treatment option for *EGFR* mutation-positive NSCLC patients who responded to short-term first-line erlotinib treatment, although the primary end point was not achieved in this study. No new safety signals were observed and the median OS in the intention-to-treat population was 53.3 months that was comparable or even better to the other combination treatment trials with EGFR-TKI and chemotherapy so far. An alternative treatment strategy to cure metastatic NSCLC patients with EGFR mutations is still eagerly anticipated.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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