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Erlotinib Treatment Beyond Progression in EGFR Mutant Patients Who Have Responded to EGFR TKIs in Stage IIIB/IV NSCLC: An Open Label Randomized Trial

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Abstract

Treatment of EGFR mutation-positive advanced Non-Small-Cell Lung Cancer (NSCLC) beyond progression using EGFR TKIs is a valid therapeutic option in oligo- or asymptomatic progression. Previous studies have shown that combination of 1st generation EGFR TKIs to chemotherapy increases Progression-Free (PFS) and Overall Survival (OS) in 1st line treatment of EGFR positive disease but the beneficial role of this combination is unproven in later treatment lines. In this open-label, phase 2 trial, we randomly assigned 18 patients with previously 1st generation EGFR TKI treated, EGFR mutation-positive advanced NSCLC in a 1:1 ratio to receive either sequential combination of erlotinib + chemotherapy (erlotinib d5-18 on 21d chemotherapy cycle) or standard chemotherapy. The primary endpoint was investigator-assessed Progression-Free Survival (PFS).

The median PFS was similar with erlotinib + chemotherapy and chemotherapy alone (4.2 *vs.* 3.4 months; CI: 3.5 to 4.8; p=0.305). The clinical benefit rate was comparable in the two groups: 66.7% with erlotinib + chemotherapy and 63.0% with standard chemotherapy (p=NS). The median overall survival was similar with erlotinib + chemotherapy and chemotherapy (9.7 *vs.* 8.3 months; 95% CI, 6.5 to 10.1; p=0.402). Adverse events of grade ≥ 3 were analogous in both groups (44.4% in both), neutropenia/neutropenic fever (33.3%) and infection (22.2%) being the most common.

The sequential combination of erlotinib + chemotherapy is a safe option in the treatment of patients who have progressed on 1st generation TKIs compared to chemotherapy alone. The primary endpoint, PFS, was consistent in both arms though statistically insignificant.

Keywords: NSCLC; EGFR mutation; Acquired resistance; Chemotherapy; EGFR TKI

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Introduction

Better conception of genetic alterations in cancer initiation and progression has led the development of diagnostic testing and targeted therapies against oncogenic driver mutations. In recent years, Non-Small Cell Lung Cancer (NSCLC) disease subsets, such as EGFR mutant (10%) or ALK translocated (3%), have been identified. Patients with these mutations are highly responsive to targeted cancer therapies [1,2]. Several randomized phase 3 studies have demonstrated the superiority of first-line EGFR Tyrosine Kinase Inhibitors (TKIs) for stage IIIB/IV NSCLC patients with activating EGFR mutations [3-9], whereas platinum based doublet chemotherapy or immunotherapy is the standard 1st line treatment for patients whose tumors do not harbor targetable mutations [10]. Besides longer Progression-Free Survival (PFS), 1st line treatment with TKIs has shown to improve response rates and QoL when compared to first-line chemotherapy in EGFR-positive NSCLC patients [9,11-13].

EGFR mutant patients are primarily refractory to the EGFR TKIs in 10% to 20% of cases, and virtually all responding patients develop acquired resistance to the treatment leading to disease progression [14-16]. The most common cause of acquired resistance is the presence of a T790M

mutation in the EGFR gene [17-19], but other mechanisms including MET amplification or PI3K mutation [20], and transformation to small-cell lung cancer may be present simultaneously [17]. T790M positive patients are generally responsive to 3rd generation EGFR TKIs like osimertinib and this is considered as a standard of care in this subset [21]. For patients with other acquired resistance mechanisms, no standard treatment is established. In general, the disease heterogeneity increases after patient has been treated with multiple lines of therapy or with very specific EGFR inhibitors, such as osimertinib, and decreases likelihood for responding to a single agent targeted therapy.

The idea of multiple heterogenic metastatic sites where some tumor sites could potentially be still sensitive to EGFR TKIs at the time of radiologic RECIST progression favors the idea of EGFR TKI treatment beyond progression [22-24], alongside with the concept of disease flare which has been described in patients after EGFR TKI discontinuation [25,26]. Many guidelines recommend considering TKI treatment beyond progression in EGFR mutant disease [10]. Treatment with TKI beyond progression is a valid option in oligo- or asymptomatic progression that can be combined to radiotherapy of the progressive tumor lesions.

Some studies have addressed combination of chemotherapy and EGFR TKIs in the 1st line setting with confounding results. Two randomized phase 3 studies have shown that combination of continuous or sequential EGFR TKI and platinum doublet improves survival of EGFR mutant patients compared to chemotherapy or single agent TKI [27,28]. Another single randomized phase 3 study has investigated use of continuous EGFR TKI with platinum-doublet after EGFR mutation positive patient has developed acquired resistance to EGFR TKI and these results did not show combinatory therapy improving progression-free survival but it even had detrimental effect on overall survival of T790M positive patients [29].

We have previously investigated efficiency of chemotherapy and EGFR TKI combinations in acquired resistance in vitro cell line models (T790M and cMET amplification) [30]. These studies showed that sequence between chemotherapy and EGFR TKIs is essential, and detrimental effects are seen especially when TKI is given immediately prior chemotherapy. Based on our in vitro models, we hypothesized that combination treatment of chemotherapy and TKI should include a wash-out period of TKI prior to chemotherapy cycle. Since chemotherapy is given in cycles, the approach should be quite feasible in routine clinical practice.

The current study investigates combination of EGFR TKI erlotinib in sequential manner with chemotherapy to chemotherapy alone in EGFR mutant patients with acquired TKI resistance. The study hypothesis is that addition of erlotinib to chemotherapy increases progression free survival.

Materials and Methods

Study design and participants

ETAP was an investigator initiated randomized two-arm, open-label, multicenter phase 2 trial of erlotinib plus either platinum doublet or single-agent chemotherapy (experimental), or chemotherapy (comparator) alone in EGFR mutant or EGFR TKI benefitting patients with stage IIIB/IV NSCLC. The study was undertaken in seven cancer hospitals in Finland.

Patients aged 18 and older, with histologically confirmed stage IIIB/IV non-small-cell lung cancer and investigator confirmed progression during EGFR TKI treatment, an activating mutation (G719A/C/S; Exon 19 insertion/deletion; L858R; L861Q) in the EGFR gene, or if EGFR mutation negative or unknown, have had at least partial response with EGFR TKI lasting ≥ 6 months, a performance status (WHO) of 0, 1 or 2, and measurable disease according to RECIST 1.1 were eligible. Disease-related exclusion criteria included previous EGFR TKI treatment beyond RECIST 1.1 defined disease progression for more than 28 days; history of hypersensitivity or intolerance to erlotinib or gefitinib or to chemotherapeutic agents used in the study. General exclusion criteria included symptomatic central nervous system metastases; unwillingness to use contraceptive during the study; known active hepatitis B or C, or HIV infection; women who are pregnant or breastfeeding; patient with uncontrolled undercurrent illness or circumstances that could limit compliance with the study; and treatment with any investigational agent for any indication within four weeks of study treatment.

The study did not include tumor re-biopsy at screening. Optional plasma samples were collected at baseline and at 8 wks.

The trial was approved by PPSHP ethics committee (55/2013, Eudra CT 2013-002049-13) and national competent authority (77/2013) and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before any study-related procedures.

Randomization

All patients who met the inclusion criteria were to be recruited in a period of 24 months from the beginning of the study. Expected number of recruited patients per arm was 40, thus the total number of patients being 80. Patients were stratified according to PS (0-1 or 2) and planned chemotherapy regimen (platinum doublet or single agent chemotherapy) and randomized into two treatment arms with block size of four. Randomization was carried out based on faxed randomization sheet at Oulu University Hospital by a study coordinator and the allocation arm was faxed back to the study center. In the experimental arm, patients received erlotinib (intermittently) + chemotherapy for four to six cycles followed by erlotinib (continuous) maintenance, and the complimentary arm consisted of four to six cycles of chemotherapy.

The primary endpoints of the study were investigator assessed progression-free survival of the whole study population and in the strata 1-2 with secondary endpoints being overall survival, objective response rate; rate of non-progression at 9 and 18 wk, and patient safety and treatment toxicity in the whole study population and in strata 1-2.

Treatment details

Patients were randomly assigned to receive four to six cycles of either platinum doublet (carboplatin AUC 5 or 6 or cisplatin 75 mg/m^2 on day 1 every three weeks with either docetaxel 75 mg/m^2 day 1, paclitaxel 200 mg/m^2 day 1, or pemetrexed 500 mg/m^2 day 1, intravenously) or single agent chemotherapy (docetaxel 75 mg/m^2 day 1 or pemetrexed 500 mg/m^2 day 1, intravenously) with or without erlotinib. In the experimental arm, the dosing of erlotinib with platinum doublet was 150 mg per day d5-18 during cycles one to three, and d5-21 on cycle four, followed by erlotinib 150 mg daily, and with single agent chemotherapy, 150 mg/day on d5-18 during cycles one to five, and d5-21 on cycle six, followed by erlotinib 150 mg daily. If patient had before study entry received gefitinib and

experienced severe EGFR TKI related side effects (rash and diarrhea gr ≥ 2), a dose lower than 150 mg of erlotinib daily could be selected by the investigator. The dose of erlotinib could be reduced in case of erlotinib-related toxicity at any point, and erlotinib treatment could either be temporarily or permanently suspended in case of serious toxicity. Study treatments were continued until disease progression or when other discontinuation criteria were met.

Tumor response was assessed by use of CT or MRI with RECIST 1.1 criteria every nine weeks. Adverse events and clinically significant laboratory abnormalities were monitored and recorded according to NCI CTCAE v 4.0. All patients were followed for survival until end of the study.

Statistical design

All patients receiving at least one complete cycle of study drug treatment are included in the eligible patient population. The primary study variable is the progression-free survival of the whole study population presented with 95% confidence intervals. The study is planned to detect clinically and statistically meaningful difference in PFS between the treatment arms. The anticipated outcome in this study is that the median PFS of the experimental arm would be six months compared to three months in the control arm. A total of 80 events randomized to 1:1 will give 65% power to confirm the superiority of the experimental arm with the use of log-rank test and two-sided significance level of 5%. Disease progression and survival information will be assessed by Kaplan-Meier estimates from the start of the study treatment to detection of PD by CT/MRI, or death at the end of the study.

Results

Study accrual and patient characteristics

Between February 4th, 2014 and May 9th, 2016, 18 patients were randomly assigned to experimental (n=9) and control (n=9) arms. All the patients received treatment and there were no losses in follow-up and all the patients were included in the final analysis. The last patient follow-up visit occurred Oct 31st, 2016. Anticipated recruitment for the study was 80 patients in 24 months. Even though the recruiting period was extended, patient accrual was stopped due to slow recruiting rate when 22.5% of the anticipated subjects were included in the study.

Patient socio-demographic and clinicopathological characteristics were generally well balanced between treatment arms (Table 1). 11 (61.1%) of the patients had platinum doublet (experimental arm n=6, control arm n=5) as chemotherapy regimen, and seven (38.9%) received single-agent chemotherapy (experimental arm n=3, control arm n=4).

EGFR mutation analysis data of the study patients is from the time of diagnosis. The study did not include tumor re-biopsies and baseline plasma samples were available only for ~50% of patients making T790M analysis non-feasible.

Adverse events

During the study, 11 (61%) patients, five (56%) in the experimental arm and six (67%) in the control arm, experienced gr3-4 NCI-CTCAE Adverse Events (AE) which were assessed to be related to study medication. The most common gr3-4 AE was neutropenia/neutropenic fever which was observed in six patients (experimental arm n=4, control arm n=2, NS), and the second most common side-effect was infection without neutropenia with three cases. Other severe AEs included pulmonary embolism (n=1) and fatigue (n=1). Four patients from the experimental arm were hospitalized, while in the control arm two patients needed hospital care. One patient in the control arm died for non-study-related cause during the study. There was no difference in gr3-4 AEs, hospitalization or death during the study between the treatment arms (Table 2).

Table 1: Patient demographics and clinical characteristics.

n=18	Chemotherapy (*n*=9)	Chemotherapy + erlotinib (*n*=9)
Female, *n* (%)	7 (78)	4 (44)
Never smoker	4 (44)	4 (44)
Mutation		
ex19 del	8 (89)	5 (56)
L858R	1 (11)	3 (33)
G719X	0 (0)	1 (11)
Initial stage IV/IIIB	9 (100)	6 (67)
ECOG		
0-1	8 (89)	6 (67)
2	1 (11)	3 (33)
Previous TKI		
Erlotinib	6 (67)	4 (44)
Gefitinib	2 (22)	4 (44)
Other	1 (11)	0 (0)
Multiple TKIs	0 (0)	1 (11)
TKI response		
PR	9 (100)	8 (89)
SD	0 (0)	1 (11)

Table 2: Safety measures according to treatment arm.

	Chemotherapy (%)	Chemotherapy + Erlotinib (%)
Gr3-4 (related)	6 (67)	5 (56)
Neutropenia/neutropenic fever	4 (44)	2 (22)
Infection	1 (11)	2 (22)
Pulmonary embolism	0 (0)	1 (11)
Fatigue	0 (0)	1 (11)
Hospitalization	2(25)	4 (50)
Death during study		
Related	0 (0)	0 (0)
Non-related	1 (13)	0 (0)

Table 3: ORR according to treatment arm.

Response	Chemotherapy (%)	Chemotherapy + Erlotinib (%)
CR	0 (0)	0 (0)
PR	2 (25)	1 (11)
SD	3 (38)	5 (56)
PD	3 (33)	3 (33)

Survival outcomes

For the whole population, the median PFS was 4.1 months (CI 3.5-4.8, NS) and median OS 8.3 months (CI 6.5-10.1) (Figure 1). In the experimental arm, median PFS was 4.2 mo (CI 4.0-4.4), and in the comparator arm 3.4 mo (CI 0.0-7.6). The median overall survival in

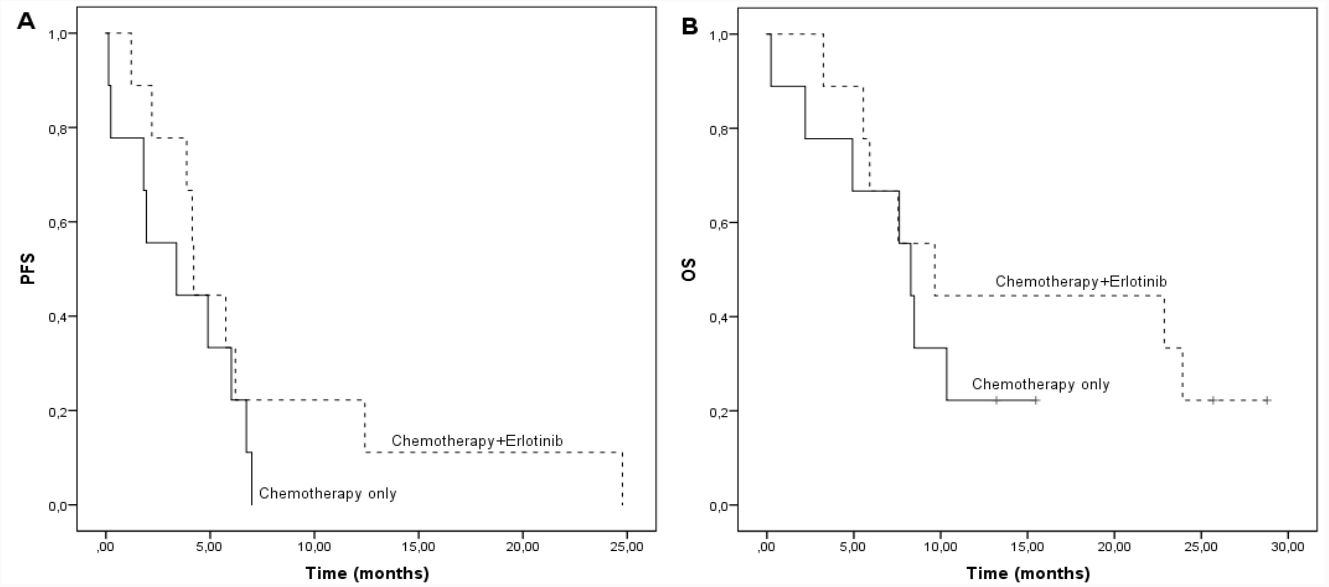

Figure 1: Kaplan-Meier analysis for progression-free (A) and overall survival (B) of all patients. Crosses indicate censored events.

the experimental arm was 9.7 mo (CI 3.5-15.8), and in the comparator arm 8.3 mo (CI 6.4-10.2).

One patient in the experimental arm and two patients in control arm achieved an objective response, while five patients in the experimental arm and three in the control arm achieved disease control. Three patients in both arms had progressive disease as a best response. None of the results were statistically significant (Table 3).

Discussion

Current study investigated the sequential use of erlotinib in combination with chemotherapy (experimental) compared to chemotherapy (comparator) alone in EGFR mutant patients with stage IIIB/IV NSCLS who had previously responded to EGFR TKIs. Due to low number of participating patients, strong conclusions cannot be made of the results. We were unable to show additional benefit of adding erlotinib to chemotherapy, but had a safety profile of the experimental therapy that was consistent with chemotherapy treatment alone.

The study was initiated 2014 and at that time, no standard of care treatment was available for EGFR mutant patients who had progressed on 1st of 2nd generation EGFR TKIs. However, later impressive results and approval of 3rd generation TKI osimertinib in T790M resistance have changed the landscape of treatment options of acquired EGFR TKI resistance [31]. Furthermore, negative results of the IMPRESS study, investigating combination of platinum doublet and daily gefitinib in acquired EGFR TKI resistance, have been published since initiation of the current study [3]. It is likely that these therapy evolutions played an important role in the slow patient accrual and ability to randomize only 22.5% of the planned patients.

Another lack of the current study is the missing information on the patients T790M status. The study did not include tumor re-biopsy at screening and baseline plasma samples were optional and available only for ~50% of patients making T790M analysis non-feasible. The IMPRESS study has shown deleterious effect of chemotherapy and gefitinib combination in T790M positive but not in the negative patients after progression on 1st line gefitinib therapy [3]. Based on the current status of acquired resistance treatment landscape, T790M status is essential for osimertinib treatment selection but it might also affect efficiency of chemotherapy and EGFR TKI combinations [32].

Even though we could not detect improvements in PFS or OS of patients receiving the combination of erlotinib and chemotherapy compared to chemotherapy alone, there was tendency for better outcomes in the combination arm for both end-points. Furthermore, we did not see increased frequency of severe adverse events in the combination arm compared to chemotherapy alone. These results suggest that approach of the current study with combination of chemotherapy and sequential erlotinib is safe and shows no signs of deleterious effects of chemotherapy and TKI combination seen in the IMPRESS study.

1st or 2nd generation EGFR TKIs have been considered as standard of care in the 1st line treatment of EGFR mutant advanced NSCLC for years. Recent results with osimertinib (FLAURA study) have shown that this treatment improves PFS compared to 1st generation TKIs with tendency for improved OS [21]. At moment, NEJ009 study, investigating combination of gefitinib and platinum doublet compared to gefitinib, is the only trial showing significant improvements of both PFS and OS compared to 1st line generation EGFR TKIs [28]. Even though similar median PFS times are seen in the experimental arms of NEJ009 and FLAURA studies, physicians and patients are likely to prefer osimertinib over combination of chemotherapy and 1st line generation TKI due to better safety profile and avoidance of iv-administrations, if economically feasible.

Treatment options are limited for patients who have progressed on osimertinib or for T790M-negative patients after 1st or 2nd generation TKIs. Even though some molecular events leading to acquired resistance, such as C797S of EGFR or c-MET amplification, have been characterized, frequencies of such specific events are low and no established, standard treatments are available [32-34]. Furthermore, tendency for increased tumor heterogeneity grows over treatment period. Low frequency of specific molecular events and increased heterogeneity of the tumor make non-targeted approach such as chemotherapy a feasible treatment option in this setting.

EGFR TKI beyond disease progression is suggested as a treatment option for patients with acquired resistance but its efficiency in combination with chemotherapy needs to be proven.

The results of the IMPRESS study showed neither deleterious effect nor benefit of adding EGFR TKI to platinum doublet in T790M negative patients. The biggest difference in the design of our study compared to IMPRESS is the sequential use of EGFR TKI (d5-18 of 21 day cycle). We have previously shown using *in vitro* acquired resistance models, that the sequence of EGFR TKI and chemotherapy has a big effect on the efficiency of the therapy [30]. The current study was designed based on our in vitro modeling which suggested that EGFR TKI and chemotherapy have synergistic effect, but this was only seen when EGFR TKI had a wash-out period before chemo. These *in vitro* findings could explain the failure of IMPRESS trial investigating the combination therapy of daily EGFR TKI with chemotherapy.

We feel that the final verdict on chemotherapy and EGFR TKI combination in the treatment of EGFR mutant NSCLC is unresolved. Positive results on PFS and OS seen on 1st line treatment with 1st generation EGFR TKIs with chemotherapy compared to TKI alone suggest that chemotherapy and TKIs can have synergistic effect [27,28]. Osimertinib has not, so far, been investigated in combination with chemotherapy. Despite the superior efficacy of osimertinib in both EGFR mutation and EGFR T790M mutation positive NSCLC patients, drug resistance is still inevitable calling for exploration of novel therapeutic solutions. In addition, the optimal sequence of distinct generation EGFR TKIs in the long-term management of patients with EGFR mutant NSCLC remains controversial. If further chemotherapy and EGFR TKI combination trials are initiated, robust preclinical validation of the dosing and scheduling of the regimen is warranted.

In conclusion, the current study investigated sequential use of erlotinib in combination with chemotherapy compared to chemotherapy alone in EGFR mutant patients with acquired resistance to 1st generation EGFR TKIs. Strong conclusions cannot be made on the study results due low accrual rate of patients. However, there were no cautionary safety signals and tendency for improved PFS and OS in the experimental arm was seen, suggesting that the approach is feasible in clinical practice.

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