CHAPTER 8B

Treatment with high-dose, weekly erlotinib in EGFR-mutated NSCLC-patients with extra-cranial progressive disease on standard-dose EGFR-TKIs

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ABSTRACT

Background: Tyrosine kinase inhibitors (TKI) provide clinical benefit in epidermal growth factor receptor (EGFR)-mutated, advanced non-small-cell lung cancer (NSCLC) patients, with reported median progression-free survival (PFS) of 12 months. Therapeutic options after development of acquired resistance are limited. An individual thoracic response on high-dose, weekly erlotinib (‘pulsatile erlotinib’) was described in a patient with resistance to TKI in standard dose. Since EGFR-TKIs are competitive inhibitors of EGF signalling, it can be hypothesized that higher doses restore sensitivity to the drug. We evaluated pulsatile erlotinib in advanced, EGFR-mutated NSCLC-patients with extracranial progressive disease on previous EGFR-TKI treatment.

Patients and methods: In a monocenter, single-arm phase II trial, advanced-stage EGFR-mutated NSCLC-patients received one dose of erlotinib 1500mg weekly. Primary endpoint was objective response rate (ORR). To minimize the number of patients being treated in the event that the regimen proves to be inefficient, Simon’s two-stage optimal design for phase II trials was applied.

Results: Eleven patients were included. ORR at 8 weeks was 9.1%. This was insufficient to continue to the second phase of the trial, which was therefore discontinued prematurely according to predefined criteria. PFS was 1.6 months. One patient remained progression-free for 10.7 months and one patient experienced a persistent clinical benefit despite disease progression according to RECIST. Toxicity comprised mainly grade 1-2; there was one grade 4 adverse event. There were no deaths.

Conclusion: Pulsatile erlotinib carries a low response rate in advanced, EGFR-mutated NSCLC-patients with resistance to EGFR-TKI. Further investigation for this indication is not recommended. Toxicity of pulsatile erlotinib is acceptable.

The study was registered with the Nederlands Trial Register (NTR; ‘Dutch trial registry’), number NTR3603.
INTRODUCTION

Lung cancer is the most prevalent cause of cancer-related death in both sexes (1). Prognosis for advanced non-small cell lung cancer (NSCLC) remains poor, although progress has been achieved in certain subcategories. NSCLC-patients with an epidermal growth factor receptor (EGFR) mutation were shown to be susceptible to treatment with EGFR-tyrosine kinase inhibitors (TKI); gefitinib or erlotinib. Despite impressive response rates of 60-70%, progression occurs inevitably after a median of 12 months (2-4).

Several resistance mechanisms have been identified, among others MET-amplification, the T790M mutation and transformation to SCLC (5-8). However, for a substantial part of these relapsing patients, the resistance mechanisms remain unknown. Often, EGFR-TKI treatment is continued beyond RECIST-progression (9). This is due to increasing evidence that patients might benefit from prolonged EGFR-inhibition beyond RECIST-progression (10-12).

Although the recommended dose for erlotinib in phase II single agent and combination trials is 150 mg once daily, doses up to 2000 mg weekly were evaluated in phase I trials and were found tolerable, with an acceptable toxicity profile (13). This higher dose of erlotinib administered in a weekly schedule (hereafter called ‘pulsatile erlotinib’) is thought to achieve higher concentrations in the cerebrospinal fluid and has been described as salvage option for patients with leptomeningeal metastases (14-18). Interestingly, a single patient refractory to standard dose erlotinib who was treated with pulsatile erlotinib therapy for leptomeningeal disease, showed an evident response of thoracic lesions as well (19).

Since erlotinib is a competitive inhibitor of EGF signalling, we hypothesized that a higher dose of the drug might theoretically restore sensitivity for the drug. If this relatively simple, higher dosing schedule is indeed effective, it would provide an easy therapeutic option for advanced, EGFR-mutated NSCLC-patients with acquired resistance to EGFR-TKI.

Hence, we initiated this trial to evaluate pulsatile erlotinib therapy as treatment option for advanced EGFR-mutated NSCLC-patients with extracranial progressive disease on standard dose EGFR-TKI.

PATIENTS AND METHODS

Study design

This study was developed as a monocenter, open-label, single-arm phase II trial. All patients provided informed consent for treatment with pulsatile erlotinib therapy according to local ethical committee regulations. The study was approved by the local medical ethical review board and was registered with the Dutch trial registry (Nederlands Trial Register, number NTR3603). The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.
Patients
Patients were recruited at the outpatient department of Pulmonary Diseases of the VU University Medical Center, Amsterdam, the Netherlands. Eligibility criteria included histologically confirmed stage IV non-squamous NSCLC-patients with an activating EGFR-mutation who progressed on erlotinib or gefinitib in daily dose of 150 mg or 250 mg respectively. Histological diagnosis was performed according to the modified WHO classification (20, 21). Patients with unknown mutation status who exhibited a documented response or stable disease to these agents for at least six months while on EGFR-TKI treatment were also eligible. Patients had to have at least one measurable disease site according to RECIST 1.1 criteria (22), WHO performance score 0 – 2 (23) and had to be 18 years or older. Exclusion criteria comprised uncontrolled infectious disease, other active malignancy, major surgery in previous 4 weeks, other treatment with investigational drugs and known prior hypersensitivity to erlotinib.

Treatment and follow-up
Patients continued previous EGFR-TKI treatment until the start of pulsatile erlotinib therapy. At start of study, oral erlotinib 1500 mg weekly was self-administered. Tablets were to be taken on the same day and at the same time every week, one hour before or two hours after the ingestion of food or other medication. Patients completed a medication diary and were instructed to inform the investigators in case of missed doses. In case of toxicity not manageable with best supportive care, treatment interruption was allowed for with a maximum of 2 weeks. Dose reductions were not allowed for. Simultaneous treatment with CYP3A4 modulator drugs was avoided. Patients received treatment until disease progression, intolerable toxicity or withdrawal of consent. On progression, further treatment was left at the discretion of the treating physician. Patients attended the outpatient clinic every four weeks for physical examination, clinical assessment and routine laboratory tests (haematology, blood chemistry and thyroid function).

Pathological assessment
Biopsies of progressing lesions were acquired prior to study initiation and analysed for histological diagnosis and mutations in EGFR (exons 18 through 21) and KRAS (exon 2 and 3) essentially as described before (24, 25). Briefly, tumour tissue was manually macro-dissected from serial sections guided by a hematoxylin eosin–stained tissue section on which the tumour was marked by a pathologist. DNA was isolated by proteinase K digestion followed by magnetic bead isolation procedure. Subsequently, DNA was subjected to high-resolution melting followed by direct sequencing of the PCR products in case an aberrant melting pattern was identified to determine the specific sequence alteration.
Study assessment
The primary endpoint was objective response rate (ORR) at 8 weeks according to RECIST 1.1 criteria (22). Secondary endpoints were PFS (time from start of treatment to documented progression of disease), disease control rate at 8 weeks (DCR; rate of no progression), toxicity and safety.

Response was measured according to RECIST 1.1 criteria (22) through contrast-enhanced computed tomography (CT)-scans of the thorax every eight weeks.

Toxicity and its severity were assessed according to National Cancer Institute Common Terminology Criteria for adverse events version 4.0 (CTC AE 4.0) (26).

Statistics
Simon’s two-stage optimal design (p0 = 0.40, p1 = 0.60, α = 0.05, β = 0.20) was applied (27), to be able to discontinue the trial in an early phase in case of insufficient activity. Initially, in the first phase up to 16 patients were maximally included. If nine patients did not meet the criteria for objective response, the treatment would be declared to be insufficiently active and would be discontinued. Otherwise, the study would continue to the second phase and recruit 30 more patients. When a total of at least 23 patients would show an objective response, the treatment would be declared to have sufficient activity to deserve further attention. Taking into account a lost to follow-up of 5%, the planned sample size was 48 patients.

All patients who received at least one dose of pulsatile erlotinib therapy were included in efficacy and safety analysis. Progression-free survival was summarized using Kaplan-Meier method with median event time and a two-sided 95% confidence interval (95% CI) for the median provided for each end point. SPSS software version 20 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

RESULTS
Patients
Eleven patients from the VU University Medical Center were enrolled between October 2011 and February 2013 and started treatment. Baseline characteristics are provided in Table 1.

Tumour response and progression-free survival
When eleven patients were enrolled in the first phase of the study, ten patients were evaluated to have progressive disease (PD) or stable disease (SD) as best response (Table 2). According to predefined criteria, this was insufficient to continue to the second phase of the trial as a maximum of six patients theoretically could have a response. The trial was therefore discontinued after the first phase. Objective response rate was 9.1% and disease control rate
was 36.4%. Median PFS was 1.6 months (95% CI, 1.3 - 2.0 months) (Figure 1). Two patients had a prolonged progression-free period; one patient was progression-free for 5.9 months and one patient was progression-free for 10.7 months.

### Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>N = 11</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(years)</td>
<td>57 (32-75)</td>
</tr>
<tr>
<td>Sex</td>
<td>female</td>
<td>11 (100.0%)</td>
</tr>
<tr>
<td></td>
<td>male</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non-smoker</td>
<td>7 (63.6%)</td>
</tr>
<tr>
<td></td>
<td>Previous smoker</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td></td>
<td>Current smoker</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Performance Score</td>
<td>PS 0</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td></td>
<td>PS 1</td>
<td>5 (45.5%)</td>
</tr>
<tr>
<td></td>
<td>PS 2</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian</td>
<td>11 (100.0%)</td>
</tr>
</tbody>
</table>

**Figure 1: Progression-free survival on pulsatile EGFR-TKI treatment**
Table 2: Response rate on pulsatile EGFR-TKI treatment

<table>
<thead>
<tr>
<th></th>
<th>N = 11</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td></td>
<td>(0.0%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>1</td>
<td></td>
<td>(9.1%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3</td>
<td></td>
<td>(27.3%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7</td>
<td></td>
<td>(63.6%)</td>
</tr>
</tbody>
</table>

Treatment

Patients received pulsatile erlotinib therapy during a median of 1.9 months (range 0.3 – 10.7). All patients were heavily pre-treated and received pulsatile erlotinib therapy as 2nd to 6th line of treatment (Table 3). All but two patients continued EGFR-TKI treatment until start of pulsatile erlotinib therapy according to protocol. These two patients were referred from another hospital where EGFR-TKI treatment had been stopped for a mean of 33 days.

There were no treatment interruptions. Progressive disease was the sole reason for discontinuation of treatment. One patient continued pulsatile erlotinib therapy after development of progressive disease according to RECIST 1.1 (one new thoracic lesion), because of an evident clinical benefit of the treatment and lack of other therapeutic options. This clinical benefit lasted for 3 months, after radiological progression.

Table 3: Lines of treatment prior to pulsatile treatment

<table>
<thead>
<tr>
<th></th>
<th>N=11</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lines before pulsatile treatment</td>
<td>1 line</td>
<td>1</td>
<td>(9.1%)</td>
</tr>
<tr>
<td></td>
<td>2 lines</td>
<td>4</td>
<td>(36.4%)</td>
</tr>
<tr>
<td></td>
<td>3 lines</td>
<td>2</td>
<td>(18.2%)</td>
</tr>
<tr>
<td></td>
<td>4 lines</td>
<td>3</td>
<td>(27.3%)</td>
</tr>
<tr>
<td></td>
<td>5 lines</td>
<td>1</td>
<td>(9.1%)</td>
</tr>
</tbody>
</table>

Pathological assessment

Eleven patients had a biopsy at time of progression on previous treatment, prior to initiation of pulsatile erlotinib therapy. Histological and mutation analysis is described in Table 4. In one patient, previously known to have an EGFR exon 19 deletion, no mutation could be detected (tumour cell percentage of this biopsy was 50%).

One patient with an exon 18 c2156G>C (p.Gly719Ala) and exon 21 mutation c2582T>A (p.Leu861Gln) remained progression-free on EGFR-TKI treatment for 11 months, after which she was referred to our hospital. A rebiopsy was performed and she was included in the trial. Interestingly, after she had started pulsatile erlotinib therapy, mutation analysis of this biopsy revealed a KRAS mutation. Since the original biopsy and rebiopsy were taken from different anatomical places, a second primary tumour could not be excluded. Unfortunately the
amount of remaining tissue was insufficient to allow for a revision or comparative genomic hybridization. The response on pulsatile erlotinib therapy of this patient lasted for 5.9 months.

Table 4: Histology and mutation status

<table>
<thead>
<tr>
<th>Initial biopsy</th>
<th>Rebiopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
<td>Frequency (%)</td>
</tr>
<tr>
<td>Histology</td>
<td>Frequency</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>11</td>
</tr>
<tr>
<td>Insufficient tumour tissue</td>
<td>0</td>
</tr>
<tr>
<td>Mutation</td>
<td>Frequency</td>
</tr>
<tr>
<td>EGFR-exon 19</td>
<td>7</td>
</tr>
<tr>
<td>EGFR-exon 21</td>
<td>3</td>
</tr>
<tr>
<td>EGFR-exon 18 + exon 21</td>
<td>1</td>
</tr>
<tr>
<td>EGFR-exon 19 + T790M</td>
<td>0</td>
</tr>
<tr>
<td>EGFR exon 21 + T790M</td>
<td>0</td>
</tr>
<tr>
<td>KRAS</td>
<td>0</td>
</tr>
<tr>
<td>No mutation in KRAS and EGFR</td>
<td>0</td>
</tr>
<tr>
<td>Insufficient tumour material</td>
<td>0</td>
</tr>
</tbody>
</table>

# First biopsy, at diagnosis
$ Rebiopsy, acquired prior to initiation of pulsatile erlotinib

Toxicity

Toxicity was acceptable in the majority of the patients. Adverse events are shown in Table 5. Nausea was the most commonly reported adverse event (63.4%). Frequency and grade of nausea were most severe on the first three days following ingestion of tablets. All were grade 1-2 adverse events, except one grade 3 liver enzyme elevation. There were no treatment deaths in this trial.

Table 5 Toxicity on pulsatile EGFR-TKI treatment

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Frequency</th>
<th>(%)</th>
<th>Grade</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>18.1%</td>
<td>Grade 1</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2</td>
<td>18.1%</td>
<td>Grade 1</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>63.4%</td>
<td>Grade 1</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>27.3%</td>
<td>Grade 1</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
<td>9.1%</td>
<td>Grade 1</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
<td>18.1%</td>
<td>Grade 1</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>1</td>
<td>9.1%</td>
<td>Grade 3</td>
<td>1</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
<td>9.1%</td>
<td>Grade 2</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>1</td>
<td>9.1%</td>
<td>Grade 2</td>
<td>1</td>
</tr>
<tr>
<td>Other *</td>
<td>3</td>
<td>27.3%</td>
<td>Grade 2</td>
<td>1</td>
</tr>
</tbody>
</table>

* ‘Other’ comprised grade 1 hemoptoe, grade 1 depression and grade 2 abdominal pain
DISCUSSION

After the successful introduction of erlotinib and gefitinib as first-line treatment in advanced, 
EGFR-mutated NSCLC-patients, there is as yet no consensus on the appropriate second line 
therapeutic strategy. We initiated this trial to evaluate the effect of pulsatile erlotinib therapy 
for extracranial progressing lesions in such patients, after having observed a response in an 
individual patient refractory for standard dose erlotinib.

There is increasing evidence that patients may benefit from continuation of EGFR-TKI 
treatment beyond progressive disease according to RECIST (11, 12, 28-30). We hypothesized 
that since some resistance mutations (e.g. T790M (31)) increase the affinity of the EGF-
receptor for ATP, theoretically a higher dose of erlotinib might overcome acquired insensitivity 
of the receptor. This is currently also being investigated in EGFR-mutated NSCLC-patients 
refractory to EGFR-TKI treatment with the T790M mutation in a phase 1 trial with high dose 
afatinib (32). However, for high dose erlotinib, in vivo results of this trial do not support this 
theory, since response rate was unsatisfying and the trial was discontinued prematurely 
according to predefined assessment criteria.

There was one patient with a partial response, whose pre-treatment biopsy revealed a 
KRAS mutation. The occurrence of a second primary tumour could not be excluded in this 
case, however this unexpected finding might be explained by the phenomenon of tumour 
heterogeneity as well (33), although KRAS- and EGFR-mutations are considered to be 
mutually exclusive (34). One other patient experienced a prolonged clinical benefit, despite 
development of progressive disease according to RECIST and benefited from pulsatile erlotinib 
for 3 additional months. RECIST criteria are widely used in clinical practice and in clinical 
trials. However, the extent to which these criteria are applicable in evaluation of response to 
targeted therapies remains controversial (35-38).

In accordance with previous results, pulsatile dosing of erlotinib was found to be safe and 
to have an acceptable toxicity profile. Adverse events were predominantly of low grade and 
no treatment interruptions or dose reductions were necessary. Despite some successes with 
pulsatile erlotinib in the treatment of EGFR-mutated NSCLC-patients with leptomeningeal 
metastases (39-42), results are conflicting (43). Given the relatively acceptable toxicity profile 
that we once again report and the absolute lack of therapeutic options for EGFR-mutated 
NSCLC-patients with leptomeningeal disease, for some of the patients with leptomeningeal 
metastases consideration of pulsatile erlotinib as therapeutic option may still be reasonable. 
However, for EGFR-mutated NSCLC-patients with extracranial progressive disease on EGFR-
TKI treatment, chemotherapy or inclusion in a clinical trial will provide better treatment 
strategies for these patients and pulsatile erlotinib should strictly be considered as ultimate 
salvage treatment (e.g. in the setting where patients refuse alternative therapies or cannot 
receive alternative therapies due to comorbidity).
An important limitation of this study was the small sample size. However, this was inherent to the statistical design and ethical consideration, thereby preventing a large group of patients being exposed to an inefficient therapy.

**Conclusion**
In conclusion, response rate of pulsatile erlotinib therapy in EGFR-mutated NSCLC-patients with extracranial progressive disease while on EGFR-TKIs was disappointing and we do not recommend this regimen for further investigation in this setting.
REFERENCE LIST


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(30) Yu HA, Sima CS, Huang J, et al. Local therapy with continued EGFR tyrosine kinase inhibitor therapy as a treatment strategy in EGFR-mutant advanced lung cancers that have developed acquired resistance to EGFR tyrosine kinase inhibitors. *J Thorac Oncol* 2013 Mar,8(3), 346-351.


High-dose, weekly erlotinib in *EGFR*-mutated NSCLC-patients


