CASE REPORT

Effective ultra-low doses of erlotinib in patients with EGFR sensitising mutation

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SUMMARY

We describe three cases of patients with advanced adenocarcinoma of the lung and epidermal growth factor receptor (EGFR) mutation treated with erlotinib 25 mg/day and 25 mg every second day, being equal to one-sixth and one-twelfth of the recommended dose. The mean age of our patients was above 70 with a WHO performance status 1 before and during the treatment. The reasons for erlotinib dose reduction were rash, diarrhoea and fatigue. The decision was a result of lack of other treatment options and radiological response on standard doses. We did not observe any liver enzyme abnormalities. However, the post-treatment creatinine increased significantly. As of February 2014, our patients are still on treatment with tolerable side effects and improved quality of life. These findings indicate that some patients responding to erlotinib with noxious side effects could have clinical benefit in doses much lower than recommended.

BACKGROUND

Patients treated with antitumour therapies often experience intolerable side effects. In the case of so-called targeted therapy, the dose–response relationship and the lowest effective doses are not definitely established. This case report is a result of an interesting and eye-opening experience of response to treatment with ultra-low doses of erlotinib in patients with lung cancer with intolerable side effects on the recommended doses.

Erlotinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) approved for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) harbouring specific activating mutations in the EGFR kinase domain.^{1 2} The National Comprehensive Cancer Network and European Society for Medical Oncology guidelines^{1 3} recommend EGFR mutation testing prior to first-line treatment in patients diagnosed with non-operable, advanced non-squamous cancer of the lung. The incidence of activating mutation is higher in the adenocarcinoma subtype (non-squamous) among never-smokers, women and people with Asian ethnicity.³ The most common sensitising mutations in the EGFR kinase domain are exon 19 deletion (over 20 variant types) and exon 21 substitution (L858R—leucine-to-arginine mutation at codon 858),^{4 5} while a point mutation in exon 20 (T790M—substitution of threonine to methionine on codon 790) is resistant to TKI.^{4 6}

Erlotinib and gefitinib are competitive inhibitors of the EGFR tyrosine kinase that reach response

rates >60% and a mean time to progression (TTP)/progression-free survival (PFS) of 12 months in patients with EGFR mutated non-squamous lung cancer.⁷ Recently, a meta-analysis also showed a significant PFS and overall survival benefit from erlotinib or gefitinib maintenance therapy after first-line chemotherapy in an unselected group of patients with advanced NSCLC.⁸ The most common adverse effects of these compounds are rash, diarrhoea and fatigue, being the major reasons for dose reduction or termination of treatment.⁹ The standard erlotinib dose (150 mg/day) coincides with the maximum tolerated dose (MTD),¹⁰ while the standard dose of gefitinib is equal to 1/3 of MTD.^{11 12} Importantly, the incidence of grades 3 and 4 rash and diarrhoea is twofold with erlotinib compared to gefitinib, and some authors speculated that it could be explained by the difference in MTD.^{12–14} However, the lowest active dose of erlotinib has not been determined, and theoretically several patients could have the benefit of even very low doses. There are only a few case reports and one retrospective study available in the literature of a low-dose erlotinib efficacy among patients with EGFR sensitising mutation.^{15–17}

In Denmark, EGFR mutation tests are routinely performed on histological or cytological material in patients with non-operable non-squamous lung cancer. At our Department of Clinical Oncology, Aalborg University Hospital, Denmark, from March 2012 to January 2013, 19 of 130 patients (14%) with non-operable non-squamous lung cancer tested positive for EGFR mutation, which is comparable to the incidence in Europe.¹⁸ Here we present three of these cases (3/19, 15%) harbouring mutation in the EGFR kinase domain, which were successfully treated with an ultra-low erlotinib dose (12.5–25 mg/day) with clinical and radiological response and with remarkable reduction of side effects.

CASE PRESENTATION**Case 1**

The first patient was an 89-year-old man with permanent atrial fibrillation, a previous smoker with a WHO performance status 1 (PS1) who was admitted to the Aalborg University Hospital in March 2012 due to dyspnoea. CT revealed right-sided pleural effusion and round infiltrates in the right upper and lower lobes. The cytological diagnosis confirmed malignant cells in the pleural effusion. The patient was diagnosed with adenocarcinoma of the lung, stage IV, T3N1M1a (according to the 7th edition of TNM),¹⁹ with EGFR deletion in exon 19. Baseline

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Figure 1 Patient 1: baseline CT before erlotinib 25 mg/day treatment.

blood samples revealed no signs of liver or kidney dysfunction. Erlotinib 150 mg/day was initiated in April 2012. Within 2 weeks, the patient had already developed a grade 3 maculopapular rash and grade 1 diarrhoea. The treatment was delayed for 14 days and after antibiotic and steroid treatment, the patient started erlotinib again, although he wished to be treated with no more than 50 mg/day.

Case 2

Our second case was a 73-year-old man, a previous smoker with pT1 NSCLC and adenocarcinoma, who was radically operated in July 2008, and diagnosed in January 2011 with bilateral multiple lung metastases and thus stage IV. The patient received six cycles of platinum-based chemotherapy (carboplatin day 1 and vinorelbine day 1 and day 8 reduced to a 75% dose from the third cycle due to neutropenia), unfortunately without response. Shortly after chemotherapy in July 2011, he was enrolled into a protocolled treatment with erlotinib 150 mg/day without a previous EGFR mutation test. Later analysis revealed an L858R mutation in exon 21. Baseline blood samples showed a normal kidney and liver function, although we noticed creatinine increase during the palliative chemotherapy with normalisation before erlotinib treatment. The patient had already developed rash, nail infection and conjunctivitis grade 1 within 7 days but continued the same dose for 3 months.

Case 3

The last patient was a 74-year-old woman, a previous smoker, who was radically operated in December 2010 for an

Figure 2 Patient 1: control CT after 3 months of erlotinib 25 mg/day treatment.

Figure 3 Patient 2: baseline CT before erlotinib 25 mg/day treatment.

adenocarcinoma of the left lobe, stage III, T1N2M0 with deletion of the exon 19 EGFR. The patient received only one cycle of adjuvant chemotherapy in 75% dose (cisplatin day 1 and vinorelbine days 1 and 8) and had to discontinue due to side effects. In December 2012, she was diagnosed with pleural metastasis and a relapse in mediastinal lymph nodes. No liver or kidney dysfunction was registered based on the baseline blood samples before the adjuvant chemotherapy and erlotinib treatment. The patient started palliative treatment with erlotinib 150 mg/day in February 2013. Three weeks later, she complained of fatigue, diarrhoea and dyspnoea. The treatment was delayed for 2 weeks and then started at 100 mg/day, but was eventually reduced to 50 mg/day 1 month later.

OUTCOME AND FOLLOW-UP

Case 1

Follow-up CT scans were performed without contrast due to increased creatinine levels after the start of erlotinib. CT scans from August 2012 and October 2012, respectively, showed partial response (PR) and stable disease (SD) according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria V1.1.²⁰ Despite good response, the patient decided to discontinue the treatment in November 2012 due to aggravated side effects such as rash, diarrhoea and fatigue. During the period from November 2012 to May 2013, the patient developed progression ([figure 1](#)). In regard to previous good response, the physician decided to try erlotinib again but with only 25 mg/day. The CT scan after 3 months of the low-dose

Figure 4 Patient 2: control CT after 3 months of erlotinib 25 mg/day treatment.

Figure 5 Patient 3: baseline CT before erlotinib 25 mg/day treatment.

treatment revealed PR (figure 2). During the next clinical follow-up, the patient complained mainly about fatigue. Rash and diarrhoea still existed but only in grade 1. Since erlotinib had a positive objective effect, the physician decided to reduce the dosage to 25 mg every second day. The CT scan from November 2013 showed progressive disease (PD) with two measurable lesions (19 and 7 mm) in the right upper and middle lobes. As the patient's PS was still 1 with tolerable side effects and improvement of quality of life (QoL), the physician decided to continue the treatment beyond RECIST progression. As of February 2014, the patient was still alive, almost 2 years after the start of erlotinib treatment.

Case 2

The control CT scan showed complete remission (CR). Unfortunately, the patient developed diarrhoea grade 3 and erlotinib treatment was paused for 2 weeks. It was then reintroduced in a reduced dose, 100 mg/day. The CT scan after three cycles showed SD. Owing to fatigue, rash and diarrhoea, erlotinib was reduced to 50 mg/day. After 6 weeks, the patient himself wanted to delay the treatment for 3 months. The next

Figure 6 Patient 3: control CT after 3 months of erlotinib 25 mg/day treatment.

CT scan showed PD (figure 3). As there was a good effect with CR after the first cycle, the physician decided to start erlotinib 25 mg/day in February 2013. After 3 months of the dose-reduced treatment, the CT scan showed PR (figure 4). The side effects became more tolerable, and reduced to grade 1 rash and fatigue. The patient is still alive and continues the treatment with erlotinib 25 mg/day with no tumour-related symptoms for 2 years and 7 months after chemotherapy for NSCLC.

Case 3

After 3 months, the control CT scan showed SD (figure 5), the patient continued erlotinib 50 mg/day despite side effects. Since rash, fatigue, recurrent skin infections, conjunctivitis and diarrhoea were interfering with the patient's activities of daily living, the physician decided to reduce the dose of erlotinib to 25 mg/day in August 2013. The control CT scan in October 2013 showed SD (figure 6). In November 2013, the patient still had diarrhoea and fatigue grade 3. Therefore, erlotinib was reduced to 25 mg every second day and the CT scan control in January 2014 showed SD. As of February 2014, the patient is still alive with tolerable side effects and no tumour-related symptoms 1 year after starting erlotinib treatment.

DISCUSSION

Targeted therapies are increasingly used for advanced lung cancer, but the optimal as well as the lowest effective doses have not been identified. Importantly, as QoL is an essential feature of such life prolonging treatment, the optimal combination of best effect with least adverse events should be determined.

Few publications have reported an effect of erlotinib with one third or lower of the recommended dose among patients with lung cancer harbouring EGFR mutation.¹⁷ This report is, to the best of our knowledge, the first to present effective use of erlotinib 25 mg every second day, being equal to one-twelfth of the standard dose.

We discuss below the common clinical and biochemical features of these patients related to the effectiveness and toxicity of ultra-low doses of erlotinib.

Age and performance status

The age of all three patients was above 70 (table 1). Although age is an important factor for treatment effect, PS is the strongest predictor right after EGFR mutation.²¹ Our patients were all PS1 before treatment and, for this reason, treated with erlotinib. Unfortunately, the knowledge of dose-response and toxicity to erlotinib within the group of elderly patients is limited as most of the practice-defining phase III trials exclude elderly patients from protocolled treatment, resulting in an average patient median age of 60.9 years.²² It is well known and observed that drug-related side effects are more common in elderly patients, and that doses need to be reduced without a physiological substrate except high age. We discuss below plausible mechanisms based on organ function and side effects of our patients.

Table 1 Patient characteristics

Patient	Age (years)	Sex	Histology	EGFR mutation	Smoking history	PS	Side effects on erlotinib 12.5–25 mg/day
1	89	M	AC	Exon 19 deletion	Pr. smoker	1	Fatigue grade 1
2	73	M	AC	Exon 21 L858R mutation	Pr. smoker	1	Rash, fatigue grade 1
3	74	F	AC	Exon 19 deletion	Pr. smoker	1	Rash grade 1

AC, adenocarcinoma; F, female; M, male; Pr. Smoker, previous smoker; PS, performance status.

Table 2 Post-treatment versus pretreatment levels of creatinine and estimated GFR (two-tailed t test)

Kidney function parameters	Patient 1	Patient 2*	Patient 3
Creatinine (increased)	p<0.001	p<0.001	p<0.001
Estimated GFR (decreased)	p<0.001	p<0.001†	p=0.0013

*Pretreatment levels of creatinine and eGFR represent measurements before erlotinib and palliative chemotherapy.

†Estimated GFR before erlotinib and palliative chemotherapy was calculated according to the MDRD study equation as the estimated GFR measurements were not available in laboratory archives before 2010.

GFR, glomerular filtration rate; MDRD, modification of diet in renal disease.

Liver and kidney function

Erlotinib is metabolised and cleared primarily in the liver and intestine by CYP3A4, CYP3A5 and, to some extent, by CYP1A2.^{23 24} Thus, elevated liver enzymes are a common toxicity and reason for dose reduction or termination of erlotinib treatment. Routine tests showed no liver abnormalities before and during erlotinib treatment and no strong CYP3A4 inhibitors (such as ketoconazole) or CYP3A4 and CYP1A2 inhibitors (such as ciprofloxacin) were prescribed. Therefore, hepatic malfunction was not a plausible cause of toxicity in our cases.

Kidney dysfunction is not regarded as a common reason for elevated erlotinib concentration or side effects, as less than 9% of a single dose of erlotinib is excreted in the urine.²⁵ Therefore, erlotinib is generally considered as a low-risk nephrotoxic agent.²⁶ However, renal toxicity has been reported after use of erlotinib²⁵ and other EGFR modulators in humans. None of our patients was primarily diagnosed with renal failure before erlotinib treatment. Nevertheless, we noted significantly increased levels of creatinine (p<0.001) with a concomitant decrease of the estimated glomerular filtration rate (eGFR, p<0.01) (table 2) compared to levels before the erlotinib treatment (figure 7). All

measurements were within the range of normal to 1.5× the upper limit of normal (1.5×ULN) and therefore estimated as grade 1 renal toxicity.²⁶ At the point of erlotinib reduction to 25 mg/day, all our patients had eGFR ~60 mL/min or lower (43–61 mL/min), indicating continuous compromised renal function.

In our report, all three patients had normal creatinine clearance and experienced a reduction of creatinine clearance simultaneously with intolerable systemic side effects shortly after erlotinib induction. The moderately reduced kidney function did not improve even with a mean dose of 12.5 mg of erlotinib daily. This could indicate that erlotinib actually affects renal function. The fact that EGF receptors are expressed in the kidney (mainly in the distal, collecting and proximal tubules, but also in glomerular capillary walls and other vascular compounds) supports this assumption.²⁶

There are no research reports about reduced kidney function after starting TKI. However, there are few studies concerning TKI tolerance in patients with manifest renal dysfunction. A phase I study of erlotinib tolerance among 54 patients with primary renal dysfunction in non-EGFR mutated tumours (only 5 with NSCLC) concluded that 150 mg seemed to be well tolerated.²⁷ In a recent case report of three patients with chronic renal failure treated with erlotinib 150 mg/day, no further renal function impairment was recorded despite a very low creatinine clearance baseline (28–37.4 mL/min).²⁸ However, these study populations were very small and not reflective of our patients regarding age and comorbidity. In our case reports, we observed a direct time dependency of increased creatinine clearance and reduced GFR after TKI start, suggesting a possible effect of erlotinib on kidney function among elderly patients.

As this is a case report of a clinical observation, only routine blood samples were analysed. Unfortunately, blood samples for erlotinib measurements were not available, which is a limitation of our report.

Figure 7 Trends in creatinine levels and erlotinib doses in time.

Smoking

The incidence of sensitising EGFR mutation is higher among never-smokers.³ Nevertheless, all three patients from our report were previous smokers but were still diagnosed with two of the most common EGFR mutations (table 1). These patients had a remarkable effect of erlotinib treatment, which supports guidelines recommending EGFR testing in non-squamous and non-operable lung cancer regardless of the patient's smoking history.²⁹

Skin toxicity, diarrhoea and fatigue

The standard erlotinib dose, 150 mg/day, is equal to MTD,¹¹ which may be the reason for the high incidence of side effects, resulting in premature treatment withdrawal. Such consequences are upsetting and disconcerting both for physicians and patients, especially when the treatment leads to response or stabilisation. Skin rash is considered predictive^{10 30} as patients with cutaneous toxicity have a higher area under the plasma concentration–time curve from time 0 to 24 h (AUC_{0–24}).¹⁰ All our patients developed rash as one of the main symptoms in the beginning of the erlotinib treatment, and two of them still had rash grade 1 at ultra-low doses of erlotinib. This indicates that all three patients had a noteworthy erlotinib plasma concentration in their blood, which could point to a defect in erlotinib clearance.

Diarrhoea and fatigue are also some of the common side effects that may lead to disruption of treatment. All three patients developed these symptoms shortly after starting TKI. However, the most persistent debilitating symptom was fatigue. Patients 1 and 3 still had fatigue at 25 mg daily, to a degree that they wanted to disrupt the treatment. At our suggestion they tried 25 mg every second day resulting in tolerable degree of both fatigue and rash. Side effects are correlated to erlotinib plasma concentration and, taken together, these findings suggest an accumulation of erlotinib in these patients.

In conclusion, we observed SD and even PR of stage IV EGFR mutated non-squamous lung cancer with ultra-low doses of erlotinib. All three patients comprise 15% of the total EGFR mutated cases (3/19). All patients were older than 70 years old, and all had intolerable side effects such as rash, fatigue and diarrhoea leading to the dose reduction. This was accompanied by a significant and stable decrease in the glomerular filtration rate. Despite the ultra-low TKI dose, all patients had grade 1 rash and/or fatigue combined with reduced kidney function but

normal liver transaminases, indicating the accumulation of erlotinib. On the basis of these observations, we speculate that erlotinib affects kidney function and excretion in elderly patients, resulting in clinically relevant effects of ultra-low doses.

In the light of this case report, it would be of value to conduct a prospective clinical trial of a low dose of EGFR-TKI in elderly patients with stage IV EGFR mutated NSCLC aiming at non-inferiority to MTD dose and improved QoL.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- Some patients with lung cancer harbouring epidermal growth factor receptor mutation can be treated with 25 mg erlotinib/day or even 25 mg every second day and still have a clinically relevant effect and tumour regression.
- Erlotinib treatment in ultra-low doses was effective and well tolerated among some elderly patients (above 70 years old) who had intolerable side effects on recommended doses.
- Erlotinib dose reduction to ultra-low doses may be a better solution than treatment discontinuation in the presence of side effects affecting quality of life.
- Erlotinib induced low-grade kidney dysfunction accompanied by clinical response in low dose erlotinib treatment.
- Fatigue was the most prominent side effect leading to ultra-low dose treatment.

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