Side-Effects of Long-Term Administration of Erlotinib in Patients with Non-small Cell Lung Cancer

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Introduction: Currently, the inhibitor of the epidermal growth factor receptor tyrosine kinase erlotinib is widely used for the treatment of non-small cell lung cancer. Patients with a mutation or deletion in the *epidermal growth factor receptor* gene will benefit most and are likely to receive the drug for long periods and willing to accept side effects if responding.

Methods: Twenty-two cases with prolonged administration of erlotinib (at least 6 months) and side effects are reported. Three cases with specific side effects are described in detail.

Results: In addition to the well-known side effects such as folliculitis and diarrhea, patients reported paronychia, fatigue, and hair changes.

Discussion: After prolonged administration of erlotinib in most patients, the initial side effects persist while other inconvenient ones may develop. This may lead to dose reductions or even cessation of treatment.

Key Words: EGFR, Erlotinib, Long term, Side effects, Fatigue.

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The inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase erlotinib became widely used after demonstrated efficacy in second- or third-line treatment of non-small cell lung cancer.[1] Because of the limited activity in the majority of the population, most patients were only treated for a few months, and therefore, mainly acute side effects were reported. This is different for patients with an activating mutation in the *EGFR* gene. Because these patients are likely to have major responses, they will receive EGFR tyrosine kinase inhibitors (TKIs) for a substantial period of time.[2] EGFR TKIs are associated with lower incidences of alopecia, nausea, vomiting, neurotoxic symptoms, and myelosuppression compared with platinum-based chemotherapy.[2] Common side effects of EGFR TKIs are folliculitis, diarrhea, dry skin, and fatigue.[1] Especially when there is a good response on treatment, patients intend to consider these side effects as tolerable. However, after months or years of treatment, some side effects may aggravate and new symptoms may occur. This may even lead to dose reduction or even premature cessation of effective therapy. In this report, we describe side effects in patients treated for more than 6 months and illustrate some of the long-term side effects of EGFR TKIs in three patients who used erlotinib for 6 months to 4.5 years.

CASE HISTORY 1

A 61-year-old Chinese woman, never smoker, presented with cognitive disturbances and coordination problems. She was diagnosed with adenocarcinoma in the right lung with two brain metastases (T2N0M1). Seven years earlier, she was treated for an adenocarcinoma in the breast. However, histology of the current lung tumor was different.

Mutational analysis demonstrated the L858R point mutation in EGFR exon 21. She was treated with whole brain and stereotactic radiotherapy. Because of a hydrocephalus, she also received a ventriculoperitoneal drain. Thereafter, 150 mg erlotinib once a day was started. Two weeks later, she developed folliculitis grade 1 of her face and diarrhea grade 1. A computer tomography (CT) scan after 6 weeks showed a significant regression of the lung tumor, and therefore, erlotinib was continued. After 5 months of treatment, the folliculitis of her face still existed but was considered too mild to treat. In addition, she showed a paronychia of the right big toe (Figure 1). Erlotinib was discontinued, and the paronychia was treated with fucidin ointment. Ten days later, the folliculitis had resolved, and erlotinib was started again at a dose of 100 mg once a day. Two months later with a persistent response of the lung tumor, the folliculitis had not recurred, but walking was still painful because the paronychia did not recover with conservative treatment.

CASE HISTORY 2

In October 2008, a 29-year-old woman with a 1-year smoking history was diagnosed with malignant pleural effusion of the right hemithorax and an adenocarcinoma in the right lung (T4N3M1). Massive pulmonary embolism was also found and treated with low molecular weight heparin.

Mutational analysis demonstrated a deletion in EGFR exon 19. She commenced with 150 mg erlotinib once a day.

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One week later, her face and thorax showed an acneiform rash. Six weeks after treatment, her pulmonary tumor regressed, and she felt good despite the folliculitis; therefore, erlotinib was continued. The dermatologist prescribed corticosteroid ointment and doxycycline for 6 weeks with good results.

FIGURE 1. Case 1: paronychia of the right big toe.

In July 2009, she complained of pain in the hair roots, an extremely dry skin and dry eyes. On her head, androgen-like frontal alopecia was visible (Figure 2), whereas hair growth on her hands, arms, and eyelashes was increased. The keratoconjunctivitis sicca was treated with methylcellulose drops. Furthermore, walking was painful because of a paronychia of the right big toe. This was treated with fucidin ointment, and the erlotinib dose was decreased to 100 mg once a day.

In October 2009, after 1-year treatment with erlotinib, her skin problems were tolerable, but she still had difficulty on walking because of paronychia. Inflammation had also started on her left toe. She was referred to the surgeon who made a wedge incision (Figure 3).

CASE HISTORY 3

In April 2005, 50-year-old man, never smoker, started with 150 mg erlotinib once a day because of a stage IV adenocarcinoma due to malignant pleural effusion of the right lung. In 2000, he was diagnosed, in another hospital, with an adenocarcinoma in the right upper lobe and underwent a lobectomy. In 2002, metastasectomy of an assumed solitary rib metastasis was performed followed within 1 year by chemoradiation for local recurrence. In 2004, he again had a local recurrence together with malignant pleural effusion. After two cycles of platinum-based chemotherapy, progression was found, and after referral to our center, erlotinib was started in April 2005.

After 6 weeks, partial remission was seen on CT scan, he felt quite good, despite a folliculitis grade 1, and erlotinib was continued. After 8 months, he complained of progressive fatigue and very dry eyes. The latter symptom was tolerable with a topical gel.

One year later, he was still using erlotinib because of persistent response, and mutation analysis of the previously resected primary tumor was performed and showed a mutation in EGFR exon 19. He was still suffering from dry eyes, a folliculitis grade 1, diarrhea grade 1, and an itching throat;

FIGURE 2. Case 2: hair before (*left*) and after (*right*) erlotinib treatment: androgen-like frontal alopecia.

FIGURE 3. Case 2: paronychia of the right big toe, and the interdigital skin is also inflamed.

however, severe fatigue had the largest impact on his quality of life.

In May 2009, there were still no signs of progression. However, after 4 years of erlotinib use, he had the same side effects, except the itching throat. In addition, he had developed erectile dysfunction, for which sildenafil was prescribed. Unfortunately, the extreme fatigue reduced the quality of life to such a degree that discontinuation of erlotinib was decided. Other causes of fatigue than erlotinib, such as anemia, electrolyte disturbances, Lyme disease, and hypothyroidism, had been excluded. After 1 week, he complained of pain in his right hemithorax for which morphine was needed to get adequate relieve. In September, an intermittent cough evolved, whereas the fatigue had improved. In December 2009, local tumor recurrence was demonstrated by CT scan and histology. Erlotinib was reintroduced at a lower dose of 100 mg once a day. Unfortunately, fatigue returned, but he was motivated to tolerate it because of the disease progression.

From 22 patients who received erlotinib for more than 6 months, we scored the side effects as reported in the patient files (Table 1). Mostly reported were folliculitis, diarrhea, keratoconjunctivitis, and fatigue. Paronychia and stomatitis were also reported in a significant number of patients. Fifty percent of patients eventually had a dose reduction because of intolerable side effects.

TABLE 1. Side Effects among 22 Patients Who Received Erlotinib for More Than 6 mo

	No. of Patients	Grade 1/2	Grade 3/4
Male/female	3/19		
EGFR deletion/mutation exon 19/21/unknown	15/5/2		
Dose reduction in months, mean (range)	15 (6–31)*		
Folliculitis	16	11	5
Diarrhea	11	11	0
Fatigue	8	7	1
Paronychia	4	1	3
Hair loss and hair changes	3	4	0
Keratoconjunctivitis sicca	6	5	1
Chronic cough	5	5	0
Stomatitis	4	4	0

EGFR, epidermal growth factor receptor.
*Among 11 patients.

DISCUSSION

Here, we describe long-term side effects in three patients receiving erlotinib for adenocarcinoma in the lung. All three had an activating mutation of the *EGFR* gene. In view of good tumor response on this EGFR TKI treatment, patients and their treating physicians were highly motivated to continue therapy. Therefore, early and continuing side effects such as folliculitis and diarrhea were considered bearable. In all cases, skin toxicity persisted. In case 2, the folliculitis resolved, but a very dry skin (xerosis cutis) occurred instead. The folliculitis in case 3 was still present after 4.5 years of treatment. In addition, diarrhea persisted in cases 1 and 3. Also, some symptoms such as paronychia, brittle hair, erectile dysfunction, and keratoconjunctivitis sicca occurred only after long-term treatment, and the latter three symptoms developed even after a year. Finally, in case 3, fatigue was increasingly a problem, eventually leading to drug discontinuation and subsequently lung cancer progression.

In the Table 1, long-term side effects among 22 patients, who received erlotinib for at least 6 months, are shown. It illustrates that most side effects were just grade 1 or 2, but because these usually persist, this may become intolerable. Eleven patients (50%) eventually received a dose reduction because of these side effects.

Several publications addressed the management of TKI-related skin toxicity.[3,4] We treated patients according to the recommendations of Galimont-Collen et al.[4] In addition, we administered loperamide for diarrhea and topical eye gel or drops for the keratoconjunctivitis sicca. Unfortunately, the paronychia often does not heal with conservative treatment,

and surgical treatment is necessary. Even this procedure may not be sufficient to walk normally again.

Erlotinib-associated skin toxicity occurs in virtually all patients who have been treated for more than 6 months, although the clinical skin spectrum changes.[5] This may be explained by the fact that EGFR is not only present in the lung tumor but also present in the skin. The EGFR-signaling cascade is involved in biology of the keratinocytes in the epidermis and the homeostasis of the hair follicles.[4] Interrupting this pathway leads to disorganization of the follicles in the seborrhoeic areas of the skin. This may lead to folliculitis, xerosis cutis, brittle hair, and paronychia.[4] Most likely, it also causes the keratoconjunctivitis sicca. Paronychia is an inflammation of the nail fold, which is difficult to treat and very disabling. A possible mechanism is chronic irritation of the thinned periungual tissue by the nail.[6] This may present as ingrown nails and often need surgical incision. Finally, there is no clear mechanism explaining the erectile dysfunction and severe fatigue. These symptoms may fit in with depression. TKI-associated depression has been reported before; however, no pathophysiologic mechanism was provided.[7] In all three patients, the dose of erlotinib was reduced to two third of the standard dose with less skin toxicity and less subjective toxicity. However, the minimal effective dose has yet to be determined in patients with EGFR tyrosine kinase mutations. We demonstrated in an earlier report that dose reduction to even one third of the standard dose may result in tumor regression.[8] Therefore, it might be worthwhile to evaluate whether the maximally tolerable dose of erlotinib, as found in early studies, is also needed in patients with activating mutations. With respect to the likelihood of prolonged treatment in these cases and therefore occurrence of the described side effects, it might be worthwhile to evaluate its efficacy at a lower dose.

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