



Cutaneous Side Effects During Therapy With Erlotinib - Case Report

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Abstract

Erlotinib is an antineoplastic drug used in the treatment of non-small cell lung cancer and pancreatic cancer. It is a potent, selective inhibitor of tyrosine kinase, a receptor for epidermal growth factor receptor (EGFR). Cutaneous side effects such as acneiform eruption, xerosis, telangiectasia, hair and nail changes are common. A case of a 70-year-old patient who developed unusual cutaneous side effects after 6 years of treatment with erlotinib was presented.

Key words: Erlotinib; Tyrosine kinase inhibitors; Dermato-toxicity.

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Introduction

In order to increase the survival rate of oncology patients and preserve their quality of life, various therapeutic modalities have been developed, such as targeted therapy, immuno-oncotherapy and hormone therapy. In this way, patients receive personalised therapy based on the unique genetic profile of their cancer. One of the targeted therapies is erlotinib therapy (Tarceva, Roche) which is directed towards the epidermal growth factor receptor (EGFR).¹

Erlotinib is an antineoplastic drug used in the treatment of non-small cell lung cancer and pancreatic cancer. It is a potent, selective inhibitor of tyrosine kinase, a receptor for EGFR. EGFR, also known as ERBB1 / HER1 is a 170 kD transmembrane glycoprotein dependent on intracellular tyrosine kinase activity that is overexpressed in different types of malignant cells. Erlotinib induces receptor phosphorylation and activates a specific set of cytoplasmic signalling molecules that reversibly block the downstream signalling pathway of the surface protein- EGFR, leading to a slowdown in the development of malignant cells

and their enhanced apoptosis. It is metabolised via CYP3A4 and excreted via the bile.¹⁻³

However, targeted therapy has not led to a reduction in the incidence of dermato-toxicity compared to standard chemotherapy, which remains a major problem as it leads to a reduced quality of life for these patients.⁴

Since EGFR is also expressed on the surface of normal cells such as basal keratinocytes of the epidermis, keratinocytes of the outer coat of a hair and on the surface of cells of the sebaceous glands, a number of side effects are expected to occur on the skin when applying this therapy. The most common of these are acneiform eruptions on the skin of the face, neck and upper torso, pruritus, ichthyosis, telangiectasias, changes in the nails such as paronychia.^{2,5,6}

The following is a case report of a patient in whom the side effects of erlotinib occurred after long-term use of this drug in the treatment of lung cancer.

Case history

A 70-year-old patient had come for her first check-up with a dermatologist in August 2020, due to extensive changes in the scalp that had first occurred 10 days before the examination. She stated that she has been treated for lung cancer for the past six years and that she uses Tarceva, reduced dose of 150 mg for lung cancer. Apart from severe itching and dry skin, she has not had any side effects from this therapy so far. After the insight into the available medical documentation in the information system of the University Clinical Centre of the Republic of Srpska, it was found that in 2014 lung adenocarcinoma with pleural metastases (pT1aNxM1, stage IV, ECOG 1) was confirmed in the patient and mutation of EGFR gene on exon 19 was detected. After the video-assisted thoracoscopic surgery (VATS) - atypical resection of the sixth segment of the lower lobe of the right lung - in 2014, the patient received chemotherapy - two doses of cisplatin plus vinorelbine - and one dose of cisplatin plus gemcitabine, after which erlotinib monotherapy in a reduced dose of 150 mg was introduced. The patient did not receive radiotherapy.

At the time of clinical examination on the scalp in the frontal part there were present numerous individual and in some places multiple confluent pustules as well as papulopustules and on the remaining part of the scalp the multiple pustules which were almost completely covered with greenish-yellow crust and individual excoriated

crusts (Figure 1 and 2). Individual excoriations were present on the rest of the skin. Subjectively, the patient complained of intense itching, pain, and burning.

After taking a swab of the skin lesion of the scalp, the patient underwent local therapy. She used



Figure 2: Numerous individual and multiple confluent pustules and papulopustules on the scalp covered with greenish-yellow crust



Figure 1: Numerous individual and multiple confluent pustules and papulopustules on the scalp covered with greenish-yellow crust

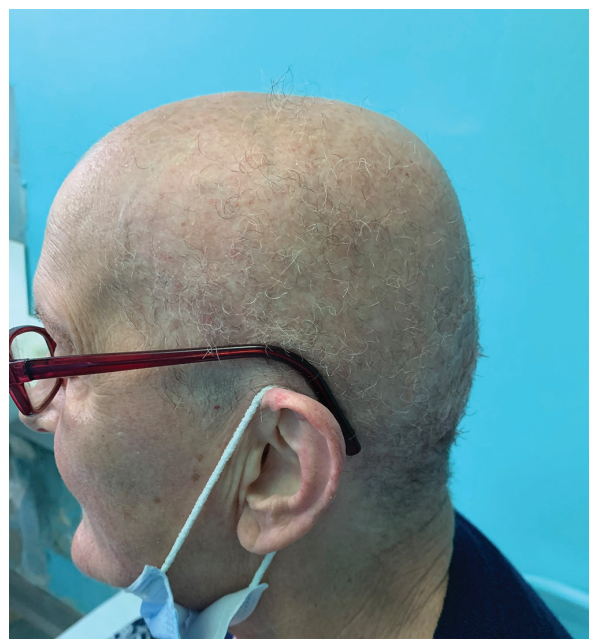


Figure 3: Complete regression of skin lesions



Figure 4: Complete regression of skin lesions

paraffin packs to remove the squama, as recommended, 2 to 3 hours before washing her hair and kerato-reducing shampoo with salicylic acid for washing her hair. Locally, she applied a 2 %-aqueous solution of eosin twice a day to the scalp, then gentamicin ointment 2-3 times a day and in the evening under occlusion. *Staphylococcus aureus* was isolated by swab and then systemic antibiotic therapy was performed according to the antibiogram, 1000 mg amoxicillin and clavulanic acid twice a day for seven days.

After 20 days at the follow-up examination there was a good regression of cutaneous changes, without any new fresh changes and crusts. The patient continued to use topical therapy of 2 %-aqueous solution of eosin and chloramphenicol. At the second follow-up examination, a complete regression of skin changes was present (Figures 3 and 4). Exclusion of erlotinib from the therapy has not been considered.

Discussion

More than 50 % of the patients who use EGFR inhibitors in their therapy develop some of the side effects on the skin.⁷ Acneiform eruptions are one of the most common side effects when applying EGFR inhibitors and they are a consequence of disorders in the proliferation, differentiation, migration of hair follicle cells.⁸ It usually occurs two weeks after the application of therapy, in contrast

to the case shown, where the eruption occurred after six years of continuous use of erlotinib.⁹

It remains unclear why this side effect occurred in the presented patient only after six years of continuous application of this therapy, in contrast to the conditions described in the available literature. Acneiform eruptions caused by erlotinib are similar to those induced by other drugs such as corticosteroids, anticonvulsants, vitamin B12 and B6, which are manifested by inflammatory papules and pustules.¹⁰

The incidence of acneiform eruptions in clinical trials varies from 33 to 79 %.⁷ Since skin rash has been confirmed to be associated with a better clinical response to applied therapy, skin rash can be used as a biomarker for a therapeutic response to EGFR inhibitors.^{11,12} However, the relationship between the occurrence of skin rash and the clinical response to applied therapy has not been elucidated.

Julian and Iwamoto¹³ proposed a mechanism of rash formation which, in addition to apoptosis of EGFR-expressing cells, is based on the interruption of the synthesis of CD45 protein expressed on the surface of hematopoietic cells. After being distributed to the bone marrow and skin, erlotinib binds to EGFR on keratinocytes, leading to their apoptosis. Apoptosis triggers an inflammatory process that leads to an increase in neutrophil production in the bone marrow with decreased CD45 expression. Due to the reduced expression, neutrophils do not have the ability to migrate towards the inflammatory process. Thus altered neutrophils will be directed towards the capillaries of the hair follicles and increase the concentration of neutrophils in these regions. Inadequate neutrophil responses and constant apoptosis of keratinocytes due to neutrophilic infiltration intensify the inflammatory process and stimulate further neutrophil production in the bone marrow.¹³

Conclusion

Dermatotoxicity is still one of the common side effects within different therapeutic modalities in the treatment of oncological conditions that can occur at any stage of treatment. Since these conditions reduce the quality of life of oncology patients, active involvement of a dermatologist during treatment is also required.

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Conflict of interest

None.

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