Acneiform rash during lung cancer therapy with erlotinib (Tarceva®)

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Abstract

Tyrosine kinase inhibitors are currently applied in the treatment of non-small cell lung cancer with overexpressed epidermal growth factor receptor (EGFR). Acneiform rash is the earliest and most characteristic side effect of EGFR inhibition. The incidence may be as high as 50-100% of cases. We report a case of a 47-year-old patient who developed acneiform rash after 1.5 weeks of treatment with erlotinib.

Key words: acneiform-rash, erlotynib, tyrosine kinase inhibitors.

Introduction

Due to the very rapid oncological therapy development we face the issue of undesired symptoms concerning, inter alia, the skin.

Erlotinib (Tarceva®) belongs to the tyrosine kinase inhibitors blocking the epidermal growth factor – EGF receptor. The EGF receptor (EGFR) is the transmembrane glycoprotein 170-kd. The EGFR expression is physiologically found in the epithelial tissues and hair follicles where it is responsible for the processes of proliferation and keratocytokines diversification [1]. Excessive EGFR expression is found in some cancers, including 50-80% of non-small cell lung cancers (NSCLC), colonic carcinomas and it is usually linked to their increased malignancy, i.e. more rapid proliferation of cancer cells, migration, stromal invasion, immunity to apoptosis and angiogenesis [2]. The EGFR inhibition may weaken the tumour growth and consequently EGFR has become an attractive target for cancer therapy development [2]. Currently, there are two groups of drugs blocking the EGF receptor: the tyrosine kinase inhibitors (gefitinib, erlotinib) and IgG 1 monoclonal antibodies against the EGF receptor (cetuximab, panitumumab) [2, 3].

Erlotinib (Tarceva®) is recommended in treatment of patients with locally advanced non-small cell lung cancers or non-small cell lung cancer with metastases in the case of which previous therapy with application of at least one chemotherapy schedule proved unsuccessful [4, 5]. Treatment effectiveness in the case of cancer patients without expression of the receptor for the epidermal growth factor (EGFR) has been shown. Erlotinib in combination with gemcitabine is recommended in treatment of pancreatic cancer patients with metastases [5].

The aim of this work was to present of a case of a lung cancer patient with acneiform rash that appeared during treatment with erlotinib (Tarceva®).

Case report

Patient aged 47 years was referred for dermatological consultation from the Ministry of Interior and Administration Oncology Centre Chemotherapy Department in July 2011 because of the scattered lesions in the form of follicular pustules, particularly extensive in the seborrhoeic areas, located on the skin of the face, trunk and extremities. In the submandibular area, layered small yellowish crusts were also present. No blackheads were found and the lesions were accompanied by itching.

A year earlier the patient was diagnosed with non-small cell lung cancer and the standard chemotherapy schedule did not give any effects; the disease progressed and metastases to the encephalon were detected. As a consequence, the patient had underwent therapy with

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erlotinib (Tarceva®) at 150 mg/day. After a week and a half from commencement of that treatment, the dissemination of pustules occurred. In the past the patient had a very mild history of acne. Following the consultation, the general treatment with tetracycline 4 × 2 tablets was applied and gel with clindamycin and benzoyl peroxide was recommended. Within 2 weeks a significant improvement and partial regression of skin lesions was recorded. The patient did not require the erlotinib dose reduction.

Discussion

The EGFR inhibitors (erlotinib, gefitinib) are usually well tolerated by the patients and do not give dangerous side effects like other cytotoxic drugs. However, they frequently cause skin lesions, most frequently in the form of acneiform rash [1, 3]. It is dependent on the dose and occurs in more than 50-100% of the patients treated with those drugs [3, 6]. In the majority of cases it does not require extensive treatment, although in 8-12% of the patients the problem is severe and may even require decreasing the EGFR inhibitors' doses [7]. They are referred to as the *acneiform rash, acneiform follicular rash, acne-like rash or maculopapular skin rash* [6].

The lesions are usually located in the skin areas rich with sebaceous glands, i.e. the face, neck, retroauricular areas, upper trunk area (V shaped) and the scalp. Sometimes the rash occurs in the lower back area, on the abdomen, buttocks and on upper and lower extremities. No lesions, however, are observed within the area of palms of the hands and feet [3, 8]. Similar lesions, but usually more intense, are observed after application of monoclonal antigens blocking the EGF receptor [8].

The rash that is itching papuloerythematous in nature transforms into pustules. The pustules may form into pus lakes that dry forming yellow crusts [3, 8]. Sometimes the lesions on the face assume the form of a spread erythema with surface pustules and telangiectasias like in the acne erythematosa. The rare image on the face resembles the seborrhoeic dermatitis. In exceptional cases, dermatitis and panniculitis with skin necrosis and black crust and ulceration may occur [3]. Absence of visible blackheads is a characteristic symptom of the acneiform rash and that is why it cannot be considered true acne. Usually the lesions are accompanied by itching, which is not observed in other drug-induced acneiform rash forms caused by corticosteroids and B group vitamins [3].

Acneiform rash develops a few days after commencement of therapy with EGFR inhibitors reaching the maximum after 2 to 3 weeks, rarely after 3 weeks (during therapy with cetuximab) [3, 6]. Usually spontaneous improvement is observed during continuation of that therapy. The lesions regress within a few weeks after termination of the therapy, sometimes leaving skin hyperpigmentation and dryness [3].

Histopathological examination of skin lesions shows the image of the neutrophil perifolliculitis within the area of hair follicles [3, 8]. Sometimes intraepidermal acantholysis is present. As opposed to true acne, there are no blackheads while the sebaceous glands are not affected by the inflammatory process [3, 6]. The pustules are sterile. In individual cases, presence of *Propionibacterium acnes* or *Malassezia furfur* has been described [3, 6].

The mechanism as a result of which the EGFR inhibition leads to acneiform rash is fully known. Physiologically, EGFR is expressed in the keratinocytes of the basic epidermis layer, external integument of the hair root in the hair follicles, sebaceous glands and eccrine sweat glands [9]. It fulfils important functions in promoting proliferation of keratinocytes, regulating the differentiation and keratinization processes. In the case of pathological conditions its excessive expression is found in squamous epithelium carcinomas, psoriasis and during wounds healing [10]. The EGFR inhibition causes disorders of keratosis processes, release of inflammatory cytokines and neutrophils recruitment [7], causing inflammation within the hair-sebaceous unit [3].

The increasing evidence exists that in patients receiving erlotinib the frequency of acneiform rash is correlated positively with the neoplasm treatment effects [7]. Appearance of acneiform rash during the therapy is considered a positive prognostic factor. In the study by Perez-Soler on 57 patients on erlotinib therapy, acneiform rash occurred in 100% of the patients with very good response to therapy, 95% with stable progress of the disease and only 75% of the patients in which disease progression was observed [11]. In support of those data, Wacker *et al.* analysed the results of pancreatic cancer patients with [12, 13] analyzed results from the National Cancer Institute of Canada Clinical Trials Group studies BR.21 [13] and PA3 (erlotinib vs. placebo in the treatment of pancreatic cancer) erlotinib at the National Cancer Institute in Canada. It was established that emergence of the acneiform rash and the level of its intensity were correlated strongly with the total length of the survival time [12, 13]. These findings have prompted some clinicians to consider the feasibility of increasing the dose of erlotinib until a tolerable rash occurs, as a rational management strategy [2, 12, 13]. Those results made some doctors consider the possibilities of increasing the erlotinib dose to causing the acneiform rash to increase the therapy effects [7].

The other skin lesions encountered during therapy with tyrosine kinase inhibitors include skin dryness like in the atopic dermatitis (4-35%), nailfold inflammation and whitlow (6-12%), disorder in growth of eyelashes and trichomegalia (5-6%) [3, 7, 9, 14], telangiectasias, hyperpigmentation [3] and hypersensitivity to sun [9].

The National Cancer Institute developed the Toxicity Criteria (NCI-CTCAE) concerning the level of intensity of the skin lesions appearing during oncological therapy. They are applied for classification of undesired events in clinical examinations, including the evaluation of undesired effects in application of tyrosine kinase application for the

Table 1. General guidelines to manage acneiform rash associated with erlotinib [7, 13]

Severity	Erlotinib	Treatment	Continuation
Mild	Continuation of drug administration at a given dose	Topically hydrocortisone 1% or 2.5% cream and/or clindamycin 1% gel	Re-evaluation within 2 weeks, if no improvement – treat as the mild grade
Moderate	Continuation of drug administration at a given dose	Hydrocortisone 2.5% cream or clindamycin 1% gel or pimecrolimus 1% cream and doxycycline 100 mg 2 times daily or minocycline 100 mg 2 times daily	Re-evaluation within 2 weeks, if no improvement – treat as the severe grade
Severe	Decrease the erlotinib dose and lesion monitoring	Treat as above in case of moderate grade and adding methylprednisolone can be considered	Re-evaluation within 2 weeks and if worse discontinuation of therapy should be considered

EGFR. In the case of those drugs the lesions are grade 2 lesions in most cases [6, 9, 13, 15]:

- grade 1 – macular or papular eruption or erythema without associated symptoms;
- grade 2 – macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering < 50% BSA;
- grade 3 – severe, generalized erythroderma or macular, papular, or vesicular eruption; desquamation covering > 50% BSA;
- grade 4 – generalized exfoliative, ulcerative, or bullous dermatitis;
- grade 5 – death.

In October 2007, a group of British experts (Erlotinib Skin Toxicity Management Consensus Group) also developed the guidelines for dealing with side effects encountered on the skin invoked by therapy with erlotinib depending on the severity of symptoms: mild, moderate and severe [7] (Table I).

Depending on the intensity of acneiform rash lesions, the topical or additionally general therapy is applied. In mild cases therapy with externally administered preparations containing antibiotics (clindamycin, metronidazole), benzoyl peroxide and pimecrolimus is recommended [7, 13]. Lack of effects was observed after topical application of retinoids, vitamin D analogues and steroids [3]. Pre-clinical data suggest good effects of applying strong phosphatase inhibitors – menadione (vitamin K_3). In a non-randomised trial, application of a cream preparation containing urea and 0.1% of vitamin K_1 reduced the lesions significantly [1, 9].

In more extensive cases of acneiform rash, general therapy with tetracyclines: oxytetracycline, lymecycline [7, 9] is used. Minocycline and doxycycline are recommended less frequently because of their photosensitivity effects [7]. Orally administered isotretinoin is not recommended because of the accompanying skin dryness and frequent symptoms of whitlow in patients. Additionally, the interaction between the isotretinoin and EGFR inhibitors is not known [3]. Antihistamine drugs (cetirizine, loratadine, hydroxyzine) are recommended to mitigate the accompanying itching [3]. Oral application of prednisolone is recommended in the case of no reaction to tetracyclines for 5 days and for not longer than 1 month only. The use of oral prednisolone was approved if the rash does not respond to systemic tetracycline therapy. Additionally, steroids may disrupt the activity of monoclonal anti-EGFR antibodies [2].

Experience within the group showed that, in cases of severe rash, the dose of erlotinib is reduced in only ~25% of patients – generally those who experience intolerable adverse effects. In the case of severe acneiform rash, the dose of erlotinib is decreased in around 25% of patients only. Discontinuation of therapy and then its reintroduction at a decreased dose when the lesions improve is practiced more frequently. A more common practice is to interrupt therapy in the worst cases and then restart it at a reduced dose when the rash has improved [7]. A key recommendation from the forum was to reassess after 2 weeks, and not stop or reduce the dose unless requested by the patient or warranted by the patient's clinical condition.

Additionally, patients treated with EGFR inhibitors should be instructed to apply emollients and sun filters (SPF ≥ 15) [7]. A key recommendation from the forum was to reassess after 2 weeks, and not stop or reduce the dose unless requested by the patient or warranted by the patient's clinical condition.

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