

Case Report

Gefitinib and Dermal Reaction: Uncovering the Path of Management

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Gefitinib induced skin reactions especially acneiform and vesiculo-bullous pustular lesion are very common particularly in summer season or the area where climate temperature is towards the higher side. Almost 50% of the patients, who take Gefitinib, develop dermal reactions. Gefitinib induced acne may be related to excessive follicular hyperkeratosis, obstructions of the follicular ostium, follicular plugging and alteration of hair cycle progression, which lead to an inflammatory response. Here, we explored different treatment possibilities for the management of these types of cutaneous reactions and also the recommendations for the use of Gefitinib therapy. Multidisciplinary treatment approach in the form of oral antibiotics and topical application with proper education to the patient to prevent or manage the dermatological reactions in patients who are treated with Gefitinib are essential in order to minimize the negative likelihood of treatment disruptions or modifications.

Keywords: Gefitinib induced dermal reactions; Cutaneous rash; Vesiculo-bullous pustular lesion

Introduction

Treatment options are limited in patients with advanced or refractory non-small cell lung cancer and lead to suboptimal outcome and/or benefit. The epidermal growth factor tyrosine kinase inhibitor, Gefitinib has been FDA approved for the treatment of non-small cell lung cancer (NSCLC) that is refractory to platinum based chemotherapy and/or second-line docetaxel therapy. In NSCLC, Gefitinib dose-dependently inhibits cellular proliferation and tumor growth and potentiates the cytotoxic effects of chemotherapy and/or radiation [1]. However, skin reactions especially acneiform, occur in more than 50% of these patients who take Gefitinib [2], and in many situations they are severe and need dose reduction or even interruption of use. In a retrospective analysis of 2-years, we present those patients who developed severe dermatological reaction on prolonged Gefitinib use. Our aim was to explore the different treatment possibilities in these patients.

Case Presentation

In a retrospective review of 2-years, 99 patients were of NSCLC (non-small cell lung cancer), out of which 25 patients were given Gefitinib therapy during the course of treatment. It was generally well tolerated but the most common adverse events noted are skin rashes, which were noted in 20% of our patients. Severe skin reactions were observed in 2 patients in form of vesiculo-bullous pustular lesion (Figure 1). These patients were taking Tab. Gefitinib 250 mg orally once daily for 6 months. They presented with a 1 month history of skin rash rapidly progressing to vesiculo-bullous pustular lesion that had developed on the extremities. Both the patients were treated with the same protocol. A swab culture from these lesions was taken, which was found to be sterile. A cutaneous reaction to Gefitinib was diagnosed. Gefitinib therapy was temporarily withdrawn and patient was treated with oral antibiotics with Tab Clindamycin 600

mg 8 hourly for 2-weeks and topical application of 2% Mupirocin ointment and a moisturizing agent. Both the patients were advised to avoid direct sunlight and heat. These skin reactions responded very well to the aforesaid treatment and Gefitinib was continued after one month of withdrawal, during the course of which they presented with fluctuating skin lesions in the form of rashes which was well managed by topical 2% Mupirocin ointment without the need for drug withdrawal (Figure-2).

Discussion

Gefitinib (ZD1839) is an anilinoquinazoline derivative, a potent and selective small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, resulting in inhibition of EGFR autophosphorylation and inhibition of EGFR signaling [1]. It is orally bioavailable and is cleared via the cytochrome P450 3A4 pathway. Many neoplasms present overexpression of EGFR, a trans-membrane glycoprotein which is involved in the stimulation of tumor growth and resistance to chemotherapy and radiotherapy treatment. Inhibitors of these receptors, or anti-EGFR, have proven to be effective in clinical trials of head & neck, colon and lung



Figure 1: Pre-treatment clinical photograph of the patient showing grade-3 vesiculo-bullous pustular lesion.



Figure 2: Post-treatment clinical photograph of the patient showing regression of the skin reactions.

cancer and have gained more and more attention in oncology [3,4]. Gefitinib is FDA-approved for treatment of NSCLC that is refractory to platinum based chemotherapy and/or second-line docetaxel therapy. However, skin reactions especially acneiform, occur in more than 50% of these patients who take Gefitinib [2], and appropriate dermatological approach is essential to satisfactorily carry on with cancer management.

Pathophysiology of Dermatological Reaction

EGFRs are mainly expressed in basal keratinocytes, sweat glands and the follicular epithelium. The possible mechanism of these cutaneous reactions may be related to the roles of EGFRs in cell differentiation, proliferation, migration, angiogenesis and apoptosis [5]. Some studies have shown a positive correlation between the incidence of cutaneous side-effects and the response to the treatment [2]. Hence, it is not necessary to stop Gefitinib treatment while managing these side-effects. The most commonly reported side effect is a distinct papulopustular rash, the incidence of which reported in the literature ranges from 53-65% [6-9]. Gefitinib induced acne may be related to excessive follicular hyperkeratosis, obstructions of the follicular ostium, follicular plugging and alteration of hair cycle progression, which lead to an inflammatory response [10]. The rash is often referred to as an acne-like or acneiform rash, due to the appearance of the lesions; however, unlike acne, a papulopustular rash is often pruritic, and affects more areas of the body, including the nose, cheeks, chin, forehead, peri-oral area, scalp, and upper trunk [11,12]. In addition, papulopustular rashes do not respond to anti-acne medications [13]. The second most common side effect was xerosis or desquamation of the face, body or distal parts of the fingers or toes (36%). Additional cutaneous side effects included multiple ingrown paronychia inflammations of the toes and fingers, small ulcers of the oral mucosa or nasal mucosa and urticaria [10]. The mechanism by which Gefitinib leads to the development of paronychia and ingrown nail remains unclear.

Description of Rash

The onset of the papulopustular rash is most commonly observed during the first one to two weeks of treatment with Gefitinib, although the range of onset reported in the literature is between two days and six weeks [11]. The rash typically progresses through four phases: phase one (weeks 0-1) begins with sensory disturbances with erythema and edema, phase two (weeks 1-3) involves eruptions of the papulopustular lesions, phase three (weeks 3-5) advances to crusting of these eruptions, and phase four (weeks 5-8) is characterized by

persistent dry skin, erythema and telangiectasias [2]. The lesions are usually sterile, but a secondary infection at the site of the eruption with bacterial or fungal origin has been described in the literature [14]. The severity of the rash waxes and wanes throughout the above described four phases, and typically resolves without permanent scarring within 2-months of therapy discontinuation, although scarring secondary to fungal or bacterial overgrowth can also occur [2,14].

Management

The overall management strategy should be individualized, depending on the type, severity, and extent of toxicity caused by the therapy and should involve a multidisciplinary clinical team. Gefitinib should be administered at their maximum tolerable doses for obtaining the most effective outcomes. Furthermore, patients should be instructed to use an alcohol-free emollient cream applied twice to thrice daily, preferably to their entire body. As per the recommendations, patient should be adequately hydrated to minimize the side effects of the drugs. Clinicians should also recommend that patients use a sunscreen with a SPF of ≥ 30 , since sun exposure may aggravate their rash [15]. Patients are strictly recommended to stay at the colder temperature and avoid the direct sun exposure, which indirectly helps to avoid the Gefitinib induced skin reactions and/or their severity. Rashes are graded according to the National Cancer Institute (NCI) criteria (NCI CTC criteria version 2.0 and 3.0).

Mild reactions (NCI-CTC grade-1) are generally localized with no associated physical symptoms. Treatment options include topical low-medium potency corticosteroids or calcineurin inhibitors (TCIs) (i.e. pimecrolimus and tacrolimus). Other options include the addition of clindamycin 1% gel to hydrocortisone 1% cream. Gefitinib should be continued while the rash is being treated [15].

Moderate reactions (NCI-CTC grade-2) are more disseminated and can include symptoms such as tenderness or pruritus. The recommended treatment is hydrocortisone 1% or 2.5% cream \pm clindamycin 1% gel, as well as a 4-week course of an oral tetracycline antibiotic, such as doxycycline 100mg or minocycline 100mg twice daily [15].

Severe reactions (NCI-CTC grade-3) are generalized with major symptoms affecting activities of daily living and are intolerable to the patient. In addition to the above measures, a short course of oral corticosteroids may be administered (i.e. methylprednisolone). Alternatively, a temporary 7-10 day discontinuation of the drug involved is recommended with subsequent reintroduction at a lower dose. Oral isotretinoin may be considered for patients who do not respond to the above measures [15]. The other recommendations in grade-3 skin lesion includes the use of oral antibiotics with Tab Clindamycin 600mg 8-hourly for 2-weeks, which even proved excellent in our present case also.

Conclusion

Skin reactions are a predictable but manageable side effect of Gefitinib, which can cause significant physical and psychosocial distress in patients, leading to decreased quality of life, and the subsequent discontinuation or disruption of therapy by either the patient or their healthcare provider [16,17]. Therefore, a timely and proactive, multidisciplinary approach in the form of oral antibiotics and topical application with proper education to the patient to

prevent or manage the dermatological reactions in patients who are treated with Gefitinib are essential in order to minimize the negative likelihood of treatment disruptions or modifications [11]. When weighing the risks and benefits of treatment, this conclusion should help to ensure that the patient's quality of life remains at the forefront of all decisions regarding dose reductions or interruptions in therapy with Gefitinib.

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