Journal of Molecular and Genetic Medicine

Rosa et al., J Mol Genet Med 2017, 11:4
DOI: 10.4172/1747-0862.1000294

Case Report Open Access

Cutaneous Toxicity from Epidermal Growth Factor Receptor Inhibitors: A Report of Two Cases

Rosa VDL[1,2], Marota EP[1], Da Mata JC[1], Sampaio MM[1] and De Oliveira JR[2]

[1]*Oncovida - Center of Oncology, Goiás, Brazil*
[2]*School of Medicine, Union of Colleges Alfredo Nasser - UNIFAN, Goiás, Brazil*

Abstract

Epidermal growth factor inhibitors are currently an essential treatment for many advance-stage epithelial cancers as colorectal and lung cancer. Although they are safe, these agents often present cutaneous adverse events that can cause dosage reduction, interruption of treatment and psychosocial discomfort. We report two cases of cutaneous toxicity in patients with solid tumors using different epidermal growth factor inhibitors.

Keywords: Solid tumors; Monoclonal antibodies; Tyrosine kinase inhibitors

Introduction

Epidermal growth factor receptor (EGFR) inhibitors are molecular-targeted agents used in the treatment of solid tumors with EGFR overexpression. EGFR is a membrane-bound glycoprotein involved in signal transduction with a key role in regulating cell proliferation and survival [1]. It is composed of an extracellular domain, a single transmembrane portion and an intracellular kinase domain. In the presence of ligand, process an interaction that results in dimerization of the receptor and activation of the kinase domain and the initiation of intracellular signaling pathways [2,3], including cell proliferation, blocked apoptosis, invasion and metastasis, and tumor-induced neovascularization [4].

There are two predominant classes of EGFR inhibitors: monoclonal antibodies that bind the extracellular domain of EGFR (cetuximab, panitumumab) and tyrosine kinase inhibitors which target the intracellular domain (gefitinib, erlotinib, afatinib) [1,5]. Although the EGFR inhibitors are associated with a variety of toxicities, including diarrhea, the most commonly seen side effect is a papulopustular rash because EGFR is highly expressed in the skin and adnexal structures [6,7]. We describe two clinical cases of patients treated with gefitinib and panitumumab respectively, with severe cutaneous toxicity.

Case Presentations

Case 1

A 68-year-old woman used geftinib for two years to second-line treatment of moderately differentiated adenocarcinoma of the lung with bone metastases that evidenced EGFR mutation. Initially, she presented good tolerance to the treatment having rash grade 1 with adequate control of the toxicity with regular use of oral antibiotics and topical steroids. In the second year of treatment, she discontinued prophylaxis and evolved with papular erythematous rash on face, scalp, neck and alopecia (Figure 1A). On this occasion the geftinib was suspended, the patient received treatment with doxycycline 100mg bid and hydrocortisone cream for 14 days with significant improvement of the eruption. EGFRI treatment was taken after 3 weeks and concomitant prophylaxis recommendation. In a long period of treatment, the patient presented partial response of the disease and clinical and quality of life improvement.

Case 2

A 74-year-old man with hypertension presented abdominal

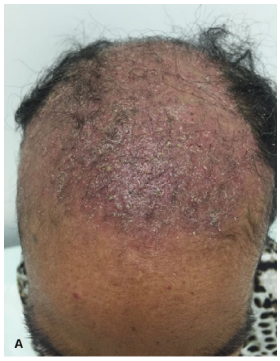

Figure 1A: Papulo-pustular rash with alopecia from geftinib (Tyrosine kinase inhibitors).

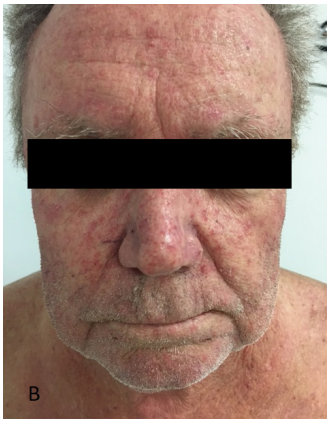

Figure 1B: Papulo-pustular rash from panitumumab (Monoclonal antibody).

***Corresponding author:** Dr. Victor Domingos Lisita Rosa, Rua 22, n.773, Setor Oeste, 74120-130, Goiânia-Goiás, Brazil, Tel: 556239968500; E-mail: victor_lisita@yahoo.com.br

Received September 26, 2017; **Accepted** October 16, 2017; **Published** October 19, 2017

Citation: Rosa VDL, Marota EP, Da Mata JC, Sampaio MM, De Oliveira JR (2017) Cutaneous Toxicity from Epidermal Growth Factor Receptor Inhibitors: A Report of Two Cases. J Mol Genet Med 11: 294 doi:10.4172/1747-0862.1000294

distention and fecaloid vomiting due to intestinal obstruction and underwent colon resection and the pathology results revealed moderately differentiated adenocarcinoma of the rectum (pathologic stage T4 N1b with negative surgical margins, NRAS and KRAS wild type). The patient was treated with 12 cycles of folinic acid, fluorouracil, and oxaliplatin (FOLFOX-4). Two years later, a computed tomography (CT) scan revealed lung metastases, and he underwent metastatsectomy so first-line chemotherapy with folinic acid, fluorouracil, and irinotecan (FOLFIRI) plus cetuximab was started. After the third cycle, the patient presented skin toxicity of the face and and was treated with oral doxycycline. The treatment was discontinued after 12 cycles due to skin toxicity and maximal response. He subsequently presented disease progression twice being exposed to FOLFOX-4 with Bevacizumab followed by Panitumumab alone. In the first month developed cutaneous toxicity mostly on the trunk and face (Figure 1B) requiring temporary interruption of treatment and dosage reduction. After treatment with oral antibiotics and topical steroids, this patient had resolution of the eruptions and maintained use of Panitumumab with good control of the disease.

Discussion

The use of EGFR inhibitors has increased considerably in recent years. EGFR inhibitors are strikingly different from traditional chemotherapy including toxicity profile. Currently, they are used in the treatment of non-small cell lung cancer, colorectal cancer, pancreatic cancer and head and neck cancer. Skin toxicity is a specific side effect of this class, which usually manifests as a papulopustular rash. The toxicity of the skin is related to the inhibition of EGFR in the healthy epidermis that is part of the normal and physiological development of the skin [8].

Papulopustular rash occurs in 80% of the patients early in the course of treatment [9-12]. Although the term "acneiform" is often used, these lesions differ from acne vulgaris in some respects. The rash manifests with papules and pustules and predominately affect face, scalp, neck, upper chest, and back [9]. Initially, there is damage to the proliferative keratinocytes in the basal layers of the epidermis following EGFR inhibition, subsequently the recruitment of inflammatory cells and macrophages mast cells and granulocytes, resulting in papulopustular rash, as well as other alterations such as periungual inflammation, xerosis and alopecia [13].

The cutaneous toxicity with EGFR inhibitors having a significant negative impact on the patient's quality of life including physical, emotional and psychosocial health and may affect compliance to treatment [14-16]. In severe cases may require dose reduction or temporary or definitive interruption therapy of treatment. Thus, adequate management is essential to avoid further episodes and suspension of treatment and to allow longer survival.

Prophylaxis with oral antibiotics, specifically minocycline or doxycycline, is recommended when initiating EGFR inhibitors [8]. The combination of steroid cream and antibiotics is recommended in the treatment of rash [17]. The use of retinoids is controversial because they may excessively dry the skin, but some authors reported having successfully reduced rashes in patients who failed to antibiotics and steroids [18].

Conclusion

We present two cases of cutaneous toxicity in patients undergoing treatment with the EGFR inhibitor. In the first image, we can visualize papular erythematous scalp lesions associated with alopecia. This patient has a diagnosis of lung cancer and has been using geftinibe for almost 2 years. The second image refers to a patient using panitubumab for treatment of metastatic colorectal cancer that presents papulopustular rash on the face and neck in the first cycle of treatment.

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