World Journal of Innovative Research (WJIR)
ISSN: 2454-8236, Volume-17, Issue-1, July 2024 Pages 01-04

Cutaneous Toxicity of Anti-EGFR in NSCLC in the National Oncology Institute of Rabat: A Literature Review and a Clinical Case

Nadir Wydad , Hachlaf Mariem , Abdi Chaimae , Lkhoyaali Siham , Mrabti Hind, El Ghissassi Brahim , Boutayeb Saber , Errihani Hassan

***Abstract*— The inhibitors of the epidermal growth factor receptor (EGFR) have revolutionized the treatment of various cancers, notably non-small cell lung cancer (NSCLC). However, their clinical utility is often hindered by their cutaneous toxicity. Within this review, we report an illustrative clinical case of a 59-year-old patient with metastatic non-small cell lung cancer treated with erlotinib. After three months of treatment, she developed grade III cutaneous toxicity, presenting as an extensive squamous-papular rash on the limbs. Management of this toxicity involved suspending erlotinib treatment for two weeks, accompanied by curative doxycycline therapy. This clinical case is discussed in light of the literature, highlighting the clinical aspects, prevalence, and management of cutaneous adverse effects associated with anti-EGFR agents.Proactive and preventive management of these side effects is essential to maximize the clinical benefits of these agents while improving patients quality of life.**

***Index Terms*— EGFR, TYROSINE KINASE, ERLOTINIB, RASH**

I. INTRODUCTION

The therapeutic revolution in oncology has been marked by the development of a new class of anticancer agents, the epidermal growth factor receptor inhibitors (EGFR inhibitors).

The epidermal growth factor receptor (EGFR), also known as ErbB1 or HER1, plays a major role in the oncogenesis of many types of epithelial-origin cancers (breast, colon, lung, head and neck, pancreas, etc.). Therapeutically, the primary targets have led to the development of anti-EGFR kinase inhibitors that act intracellularly, such as erlotinib, gefitinib, and lapatinib, as well as monoclonal antibodies that act extracellularly, such as cetuximab and panitumumab. Pharmacologically, EGFR inhibitors have very few hematological consequences, unlike conventional chemotherapy. However, cutaneous reactions are frequent, varied, and sometimes significant and debilitating. These reactions mainly include a papulopustular rash, which is by far the most common side effect, with an incidence reaching up to 80% of patients. (1)

The aim of this work is to report a clinical case of cutaneous toxicity secondary to erlotinib, its psychological impact, and its effects on therapeutic follow-up, along with a review of the literature on management.

II. CASE REPORT

This is a 59 year old patient , PS 1 ,has no comorbidity , no smoking and no history of allergies. She is followed for stage IV pleural and bone lung adenocarcinoma, PDL 1 to 0%, mutated EGFR (L858R MUTATION of exon 21) treated with ERLOTINIB at a dose of 150 mg per day continuously, after 03 months of treatment appearance of rash with desquamation on the face and nasolabial folds (Figure 1), papulo-squamous lesions hand , arm (Figure 2) and on the feet (Figure 2) The clinical examination do not found other signs . treatment with ERLOTINIB, TARCEVA was suspended for two weeks with doxcycline taking a dose of 100 mg per day for 06 weeks with emollient cream, antihistamine and sun protection, we note a good clinical evolution with regression of the lesions after 03 weeks of treatment then complete resolution of the lesions after 4 weeks with resumption of treatment with ERLOTINIB at 150 mg per day.

The radiological evaluation after 03 months of treatment was favorable hence the continuation of TARCEVA at the same dose of 150 mg per day orally associated with preventive treatment with doxycicline 100 mg per day.

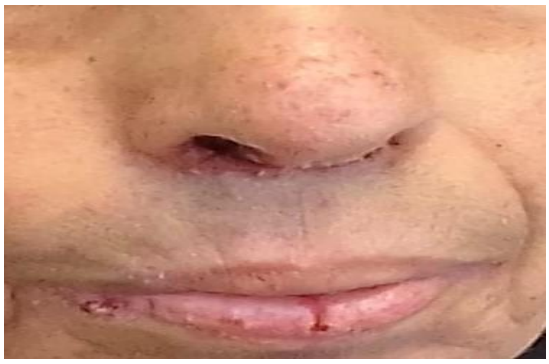

Figure 1 : Nasolabial folds

NADIR WYDAD , Department of Oncology, National Institue of Oncology, Rabat, Morocco
HACHLAF MARIEM , Department of Oncology, National Institue of Oncology, Rabat, Morocco
ABDI CHAIMAE , Department of Oncology, National Institue of Oncology, Rabat, Morocco

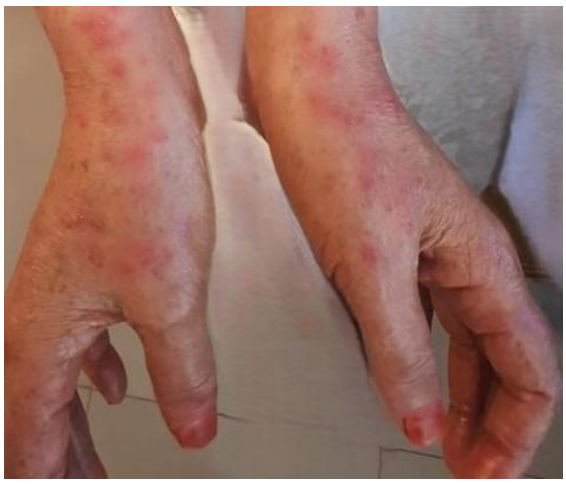

Figure 2 : Papilary squamos rash

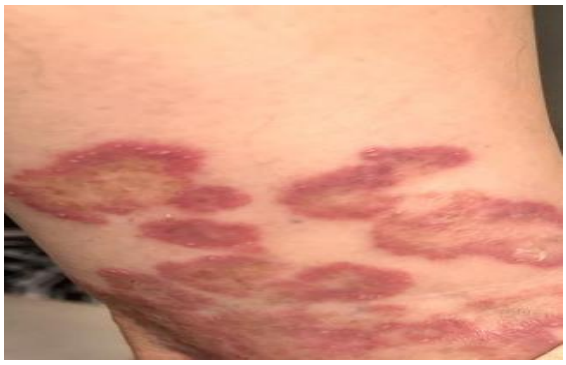

Figure 3 : Papilary squamos rash

III. DISCUSSION

Lung cancer is the leading cause of cancer-related death worldwide, accounting for the highest mortality rates in both men and women , Smoking is the leading cause of lung cancer, responsible for approximately 85% of all cases.

Lung cancer constitutes a significant public health problem, causing a considerable number of deaths worldwide. GLOBOCAN 2020 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer (IARC) show that lung cancer remains the leading cause of cancer deaths, with approximately 1.8 million deaths (18%) in 2020. [2]

A mutation in the EGFR gene can be found in approximately 10% of NSCLCs in the Caucasian population. This mutation is mainly found in women, adenocarcinomas and non-smokers. Women are therefore the group that benefits the most from targeted anti-EGFR (tyrosine kinase inhibitor: TKI) therapies. [3]

The epidermal growth factor receptor (EGFR) is found in the vast majority of non-small-cell lung carcinomas (NSCLCs). EGFR plays a crucial role in regulating both proliferative and survival signaling pathways involved in carcinogenesis, invasion, and metastasis. It has been identified as a factor influencing metastatic potential and serves as both a predictive [4–5] and prognostic factor [6–7]

EGFR is a transmembrane receptor of the tyrosine kinase type, belonging to a family of four structurally similar proteins. To date, several ligands of EGFR have been identified, enabling its activation and dimerization, ultimately leading to autophosphorylation of its intracellular domain. This biochemical modification triggers a cascade of intracellular signaling that regulates tumor proliferation, local and distant invasion, resistance to apoptosis, and neo-angiogenesis.[7] . Erlotinib prevents autophosphorylation and blocks the tyrosine kinase signaling pathway by binding to the catalytic domain of the tyrosine kinase.

Several clinical trials, including the phase III EURTAC trial and the ENSURE trial, have shown improved progression-free survival compared to the chemotherapy-treated group in non-small cell lung cancer Additionally, the OPTIMAL randomized trial demonstrated improved overall survival. .[8-9]

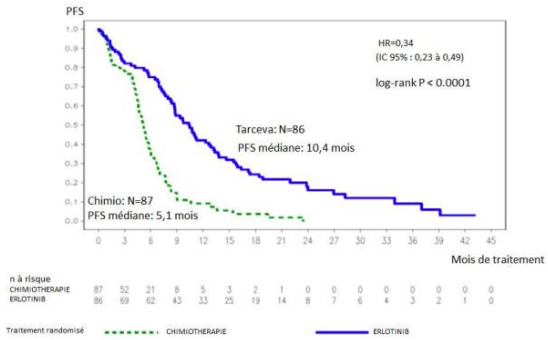

Figure 4 : Kaplan-Meier curve of PFS assessed by the investigator in the ML20650 trial (EURTAC) [9]

Erlotinib has led to advances in the treatment of metastatic non-small cell lung cancer. Its oral form promotes better compliance and offers greater therapeutic flexibility for patients. Although this treatment has fewer side effects than chemotherapy, it requires monitoring, particularly skin side effects which can be disabling for patients.

In clinical trials with EGFR inhibitors, rashes are for the most part classified concurring to the National Cancer Established Common Harmfulness Criteria (NCI-CTCv2.0, 3.0) [10].

Skin damage is the major side effect of anti-EGFR treatment, unlike chemotherapy treatments (Table 1) These skin lesions are classified by grade, from 1 to 4, in order to better understand and manage this toxicity. Most patients treated with EGFR inhibitors experience grade 1–2 rashes, while more severe reactions are rare . Studies have shown that patients treated with cetuximab, erlotinib, and panitumumab, regardless of rash grade, had greater survival than patients without rash, with patients with grade 3 rash having the longest survival [10-11].

	Erlotinib (n=84)			Standard chemotherapy (n=82)			p value for grade 3–4
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	
Fatigue	43 (51%)	5 (6%)	0	43 (52%)	16 (20%)	0	0·0086
Rash	56 (67%)	11 (13%)	0	4 (5%)	0	0	0·0007
Diarrhoea	44 (52%)	4 (5%)	0	15 (18%)	0	0	0·1206
Appetite loss	26 (31%)	0	0	26 (32%)	2 (2%)	0	0·2425
Anaemia	9 (11%)	0	1 (1%)	37 (45%)	3 (4%)	0	0·3644
Neutropenia	0	0	0	15 (18%)	12 (15%)	6 (7%)	<0·0001
Alopecia	12 (14%)	0	0	13 (16%)	2 (2%)	0	0·2425
Neuropathy	7 (8%)	0	1 (1%)	11 (13%)	1 (1%)	0	1·0000
Arthralgia	8 (10%)	1 (1%)	0	4 (5%)	1 (1%)	0	1·0000
Thrombocytopenia	1 (1%)	0	0	1 (1%)	6 (7%)	6 (7%)	0·0003
Aminotransferase rise	3 (4%)	2 (2%)	0	5 (6%)	0	0	0·4970
Febrile neutropenia	0	0	0	1 (1%)	1 (1%)	2 (2%)	0·1183
Pneumonitis	0	1 (1%)	0	0	1 (1%)	0	1·0000

Table 1 : Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria version 3.0.1 [10].

The additional dermatological effects of EGFR inhibitors include the possible development of paronychia, a painful inflammation of the proximal and lateral nail folds of the toes and fingers, with the thumbs and big toes being more frequently affected. these lesions do not represent a constraint to the continuation of the treatment.

So far, the mechanism behind the appearance of these skin lesions remains unknown. It appears to be linked to an inflammatory response resulting from cellular changes induced by the action of anti-EGFR agents.

There is no standard of treatment for secondary folliculitis; approaches vary depending on the experience of practitioners. A group of French experts, including dermatologists and an oncologist, named PROCUR, has developed therapeutic algorithms for the management of these skin lesions [12].

in practice, preventive measures make it possible to reduce the incidence of grade 3 and 4 skin rash and consist of taking doxycycline at a dose of 200 mg/day and an emollient cream, at the introduction of the treatment by anti-EGFR with sun protection to avoid photosensitivity induced by cyclins. Experts believe that the effectiveness could be equivalent with doxycycline at a dose of 100 mg/day or lymecycline at a dose of 300 mg/d , the proposed curative treatment is based on the severity skin lesions defined by version 4.0 of the CTCAE [13-14]

The curative treatment of folliculitis is the continuation of doxicycline at a preventive dose for 06 weeks, class II and III topical corticosteroids are indicated in grade 2 and 3 rash .

The most frequently observed adverse events in patients treated with Tarceva in studies BO18192 and BO25460 were skin rash and diarrhea . No grade 4 skin rash or diarrhea was observed in either of these studies. In study BO18192, Tarceva was discontinued due to skin rash and diarrhea in 1% and < 1% of patients, respectively, while in study BO25460, no discontinuations due to skin rash or diarrhea occurred. Dosage modification (discontinuations or reductions) was necessary due to skin rash or diarrhea in 8.3% and 3% of patients, respectively, in study BO18192, and in 5.6% and 2.8% of patients, respectively, in study BO25460. [15].

IV. CONCLUSION

In conclusion, EGFR inhibitors have revolutionized the treatment of non-small cell lung cancer (NSCLC), providing an effective and well-tolerated alternative thanks to their oral administration. Studies have clearly demonstrated the effectiveness of these treatments, but their use is often associated with significant skin side effects. Initial management of these effects relies on prevention, thus emphasizing the importance of careful monitoring by practitioners. Early identification of skin symptoms and implementation of preventive measures can avoid the need to suspend or reduce doses, thereby preserving therapeutic effectiveness while limiting the psychological impact on patients. This approach highlights the need for close collaboration between patients and healthcare professionals to ensure effective and well-tolerated treatment in the fight against NSC .

ACKNOWLEDGMENT We thank our oncologist's colleagues at national institute of oncology of Rabat who provided care and support for the patient

REFERENCES

[1] Pérol, M., & Arpin, D. (2007). Les inhibiteurs de tyrosine kinase de l'EGFR dans le traitement du CBNPC. Revue des Maladies Respiratoires Volume 24, numéro 8, partie 2, octobre 2007, pages 188-197
[2] Organisation Mondiale de la Santé , 12 août 2023
[3] Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small cell lung cancer (EURTAC) : A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46
[4] Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129–39.
[5] Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science 2004;304:1497–500.
[6] Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 2004;101:13306–11.
[7] Hirsch FR, Varella-Garcia M, Bunn Jr PA, Di Maria MV, Veve R, Bremmes RM, et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. J Clin Oncol 2003;21: 7398.
[8] Lancette Oncol. Mars 2012;13(3):239-46. est ce que je: 10.1016/S1470-2045(11)70393-X. Publication en ligne le 26 janvier 2012.
[9] Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L.al , Ann Oncol. Septembre 2015;26(9):1877-1883.
[10] Rosell, R., Carcereny, E., Gervais, R., Vergnenegre, A., Massuti, B., Felip, E., … Sanchez, J. M. (2012). Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. The Lancet Oncology, 13(3), 239–246. doi:10.1016/s1470-2045(11)70393-x

[11] Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Versionhttp://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf (accessed Jan 11, 2011).

[12] Bachmeyer C, Reguiaï Z, Peuvrel L, Bachet JB, Bensadoun RJ, Ychou M, André T, Bouché O, Dréno B. Toxicité cutanée des anti-EGFR (epidermal growth factor receptor) : algorithme thérapeutique du groupe franc¸ais PROCUR. Bull Cancer 2013 ; 100 : 417-26. doi : 10.1684/bdc.2013.1735.

[13] NCI Common Terminology Criteria for Adverse Events (CTCAE), v4. ctep.cancer.gov/reporting/ctc.html.

[14] Chan A, Tan EH. How well does the MESTT correlate with CTCAE scale for the grading of dermatological toxicities associated with oral tyrosine kinase inhibitors? Support Care Cancer 2011 ; 19 : 1667-74

[15] Cappuzzo, F., Ciuleanu, T., Stelmakh, L., Cicenas, S., Szczésna, A., Juhász, E., … Giaccone, G. (2010). Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. The Lancet Oncology, 11(6), 521–529. doi:10.1016/s1470-2045(10)70112-1