Editorial

Skin communicates what we deeply feel: antibiotic prophylactic treatment to reduce epidermal growth factor receptor inhibitors induced rash in lung cancer (the Pan Canadian rash trial)

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) represent a major breakthrough for patients with metastatic lung adenocarcinoma primarily exhibiting an *EGFR*-activating oncogenic mutation. The ability of EGFR inhibitors to block specific molecular pathways driving uncontrolled cellular division in cancer has resulted in a decreased incidence of serious systemic adverse events commonly associated with conventional cytotoxic chemotherapy. However, due to the abundant expression of EGFR in the skin and adnexal structures, cutaneous adverse events (CAEs) to EGFR inhibitors are frequent (1).

Acneiform eruption is the prototypical cutaneous adverse reaction associated with all EGFR inhibitors. Acneiform eruption is rarely life-threatening, but it affects cosmetically sensitive areas, causes pain and pruritus, and may impair the quality of life (QoL) of the patients and adherence to cancer therapies. In intolerable or severe cases, dose modification or interruption of a potentially life-prolonging therapy may be necessary (2).

The pathophysiology of the TKIs cutaneous toxicity is not clearly understood. EGFR inhibition blocks signaling pathways, preventing keratinocytes from properly maturing and altering migration to the outer stratum corneum. The effects result in the thinning of the outermost layers of the epidermis and corneal layers, with subsequent loss of the protective barrier function of the skin, increasing sensitivity to UV radiation damage (3,4). The cutaneous toxicity mainly affects high-content of sebaceous zones, eccrine glands, and other areas with a high EGFR expression (basal layer of dermis and pilosebaceous follicle). Recent findings in animal models have shed light on a previously underestimated role of EGFR in immune cells that might be targeted by systemic EGFR inhibition (5). Histological analysis of skin rash showed mainly CD4-positive T cells and CD1a-positive Langerhans cells throughout the dermis and epidermis, whereas the lesional dermis was dominated by mononuclear myeloid cells like macrophages and activated dendritic cells. Of note, neutrophils were predominantly located at distorted hair follicles (6). In mice deficient for EGFR in basal epidermal keratinocytes (EGFR-DEP) the resident immune cell populations of the epidermis, Langerhans cells and γδ T-cells, progressively disappeared from the epidermis and were replaced by inflammatory DC and αβ T-cell populations, whereas in the dermis mainly macrophages and mast cells accumulated (7). Increased expression of the death receptor ligand TNF-related apoptosis-inducing ligand (TRAIL) in cells infiltrating into the dermis that might contribute to rash development has been also reported. The inflammatory infiltrate is likely triggered by primary changes in epidermal epithelial cells and maintained by secondary infections and barrier defects (8). Recent research demonstrates that treatment of human keratinocytes with erlotinib reduced expression of *Human Beta Defensin 3* (*hBD3*), *Ribonuclease A Family Member* 7 (*RNase7*), and *Human cathelicidin antimicrobial peptide* (*CAMP*); similarly, alters

expression of β-defensin and S100 proteins (regulates the transcription of S100A2 and S100A7) promoting infection by *Propionibacterium acnes* and *Staphylococcus aureus*, both susceptible to antimicrobial control (9).

The management of the acneiform eruption for each patient should be individualized, based upon the type, severity, and location of the lesions, and the necessity of continuing treatment with EGFR inhibitors. Management in consultation with a dermatologist is suggested for most patients. The latter is particularly necessary if the skin reaction does not improve within two weeks of treatment, or if it is severe (grade 3 to 4), or has an atypical appearance or distribution (10). Tetracyclines have been widely used as a treatment for rash, due to their anti-inflammatory properties through inhibition of lymphocyte proliferation, neutrophil migration, and interleukin-6 synthesis, as well as their antibacterial properties conferred by binding to the 30S ribosomal subunit in the mRNA translation complex (11). It has been suggested that the beneficial effect of tetracyclines responds to the inhibition of *Propionibacterium acnes* accompanied by a reduction in sebum free fatty acids and extracellular lipases. Thus, the therapeutic effects of tetracyclines in acne may at least be in part due to reduction in neutrophilic chemotaxis, as well as their inhibitory effect on proinflammatory cytokines and MMP-9 (gelatinases B) which contribute to tissue destruction (12).

In the article that is the object of this editorial, Melosky *et al*. (13) report negative results when considering the primary objective, because there was no difference in the incidence of rash using antimicrobial prophylaxis or reactive treatment, for any grade, in any of the three arms, with rates of 82% to 84%. An unplanned secondary analysis revealed that reactive treatment did not significantly increase time to the maximal toxicity, compared with the control arm (13.3 *vs*. 12.0 days, respectively). Conversely, preemptive treatment was efficacious in delaying maximal rash, compared with the two other arms together (17.4 days, P=0.014). The authors did not observe any difference in terms of QoL, as analyzed using of the Dermatology Life Quality Index, a practical 10-question validated QoL questionnaire (13).

The preemptive treatment for EGFR TKI-induced skin reactions, delayed the occurrence of maximal rash and decreased the incidence of grade 3 rash, regardless of the treatment schedule; yet, the patients still did not feel their QoL had improved, despite experiencing less severe dermatological AEs. In the trial, patients had scheduled visits to oncologists every 4 weeks and used a diary to record rash occurrence. It is possible that patients who received reactive treatment and then developed a grade 1 or grade 2 rash did not visit their oncologists for treatment, because they were instructed "to see their doctor if the rash became intolerable." Thus, the rash could have been considered tolerable, yet still impairing QoL because it was chronic, suggesting a major difference in point of view between physicians and patients. The initial hypothesis of a 25% incidence of rash in the prophylactic treatment arm and a 50% incidence in the two other arms clearly overestimated the efficacy of dermatological treatments, because the true incidence of any grade of rash observed was more than 80%. Thus, it is possible that the trial was underpowered to detect any difference. The trial failed to demonstrate the superiority of prophylactic treatment in terms of rash incidence, although it did provide some objective data supporting the relative efficacy of treatment administered only when the first dermatological sign appears.

In contrast, in a trial conducted by our group the patients had a similar toxicity profile as previously reported with afatinib and other TKIs, however, one of the biggest advantages is the fact that patients were evaluated systematically by a dermatologist specialized in cancer that performed a complete description of all skin toxicities to afatinib (14). We found that rash incidence and severity (grade ≥2) diminished in the tetracycline group. Additionally, we observed a reduction in paronychia (37.8% *vs*. 28.9%) and folliculitis (28.9% *vs*. 20%); however, this was not statistically significant. These results reinforce the conclusion that tetracycline is effective as preemptive and curative treatment for patients who develop skin toxicities. In the article that accompanies this editorial, treatment with minocycline did not significantly reduce folliculitis incidence induced by erlotinib, but did reduce its severity. Most of the patients developed the maximum rash intensity between weeks 1 and 4, after treatment administration. Therefore, the very moment when patients start receiving tetracycline plays an important role in the incidence of skin toxicities None of the patients developed toxicities secondary to tetracycline because it was a relatively low dose, which makes these drugs safe in this group of patients. Despite that, tetracycline reduced the rash severity grade ≥2, this did not affect in the decision of afatinib dose reduction, some patients can interrupt the administration of TKI secondary to other toxicities (e.g., gastrointestinal toxicities) (15,16).

Compared with our results, this could be explained by the higher frequencies of rash with afatinib, compared with erlotinib (17), with a notorious effect of the preemptive treatment with tetracycline in this group of patients.

Besides, Jatoi *et al*. found that prophylactic tetracycline does not diminish rash severity induced by an EGFR inhibitor, but these negative results might be explained by the reduced number of patients, as well as the wide heterogeneity in type of cancer diagnosis (including patients with gastrointestinal tumors, lung cancer, and other neoplasms) and treatment (most of the patients received cetuximab and only one patient received TKI-EGFR) (18).

Other randomized study evaluated preemptive skin treatment including doxycycline in patients with metastatic colorectal cancer who received panitumumab—an anti EGFR antibody—demonstrating a reduction in the incidence of grade ≥2 skin toxicities; nevertheless, this study evaluates skin toxicity induced by monoclonal anti-body directed to EGFR and not with TKI-EGFR as shown in our study (19).

Another randomized phase II trial in lung cancer patients treated with dacomitinib, an oral irreversible pan-HER inhibitor by Lacouture *et al*. also investigated the effect prophylactic doxycycline. The results of this study were in similar manner as the ones from our group, with reports of a significant reduction in the incidence of grade ≥2 CAEs by 50% (P=0.016) (20).

Reducing the incidence and severity of these events is important. Moreover, in a setting in which patients treated with a TKI may develop resistance and may need combined treatments that can trigger skin toxicities, such as cetuximab plus afatinib (21). Then, it is necessary to have a treatment option for these CAEs, without decreasing the benefit of this combination. It has been previously reported that rash can be a surrogate of treatment benefit with a TKI (21). In our study we did not observe any relationship between skin toxicities and outcomes, but this could be explained because treatment with tetracycline may modify the pathophysiology of these toxicities, reducing their incidence and severity. At the same, the use of tetracycline did not seem to affect afatinib outcomes.

Since treatment with target therapies is expensive, the development of severe skin toxicities can increase the costs of management. Therefore, less expensive, preemptive strategies to diminish skin toxicities are necessary and may be beneficial for patients (22,23).

The article object of this editorial shows that the prophylactic or symptomatic CAEs treatment in non-small cell lung cancer (NSCLC) patients in spite of not diminishing the incidence of acneiform eruption, it reduces its severity, most importantly without compromising its efficacy. Therefore, both treatments are a good option in patients treated with erlotinib. Moreover, it is important to consider that with the advent of newer drugs in oncology, such as anti-EGFR therapies, newer toxicities that impair QoL are likely to develop and preemptive treatments may help in treating these types of toxicities. In conclusion, even if the article failed to find a benefit for preemptive minocycline, several articles have reported that the use of oral tetracyclines is a cost-effective measure that reduces the incidence and severity of rash associated to EGFR-TKIs, apparently more effective in second generation TKIs as afatinib and dacomitinib.

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Footnote

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Comment on: Melosky B, Anderson H, Burkes RL, *et al*. Pan Canadian Rash Trial: A Randomized Phase III Trial Evaluating the Impact of a Prophylactic Skin Treatment Regimen on Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor-Induced Skin Toxicities in Patients With Metastatic Lung Cancer. J Clin Oncol 2016;34:810-5.

References

1. Hu JC, Sadeghi P, Pinter-Brown LC, et al. Cutaneous side effects of epidermal growth factor receptor inhibitors: clinical presentation, pathogenesis, and management. J Am Acad Dermatol 2007;56:317-26.
2. Jatoi A, Nguyen PL. Do patients die from rashes from epidermal growth factor receptor inhibitors? A systematic review to help counsel patients about holding therapy. Oncologist 2008;13:1201-4.
3. Segaert S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. Ann Oncol 2005;16:1425-33.
4. Hammond-Thelin LA. Cutaneous reactions related to systemic immunomodulators and targeted therapeutics.

Dermatol Clin 2008;26:121-59, ix.
5. Zaiss DM, van Loosdregt J, Gorlani A, et al. Amphiregulin enhances regulatory T cell-suppressive function via the epidermal growth factor receptor. Immunity 2013;38:275-84.
6. Brodell LA, Hepper D, Lind A, et al. Histopathology of acneiform eruptions in patients treated with epidermal growth factor receptor inhibitors. J Cutan Pathol 2013;40:865-70.
7. Mascia F, Lam G, Keith C, et al. Genetic ablation of epidermal EGFR reveals the dynamic origin of adverse effects of anti-EGFR therapy. Sci Transl Med 2013;5:199ra110.
8. Guttman-Yassky E, Mita A, De Jonge M, et al. Characterisation of the cutaneous pathology in non-small cell lung cancer (NSCLC) patients treated with the EGFR tyrosine kinase inhibitor erlotinib. Eur J Cancer 2010;46:2010-9.
9. Holcmann M, Sibilia M. Mechanisms underlying skin disorders induced by EGFR inhibitors. Mol Cell Oncol 2015;2:e1004969.
10. Peréz-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? J Clin Oncol 2005;23:5235-46.
11. Sun V. Management of treatment-induced dermatologic toxicities in palliative care. J Hosp Palliat Nurs 2012;14:80-5.
12. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. J Am Acad Dermatol 2006;54:258-65.
13. Melosky B, Anderson H, Burkes RL, et al. Pan Canadian Rash Trial: A Randomized Phase III Trial Evaluating the Impact of a Prophylactic Skin Treatment Regimen on Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor-Induced Skin Toxicities in Patients With Metastatic Lung Cancer. J Clin Oncol 2016;34:810-5.
14. Arrieta O, Vega-González MT, López-Macías D, et al. Randomized, open-label trial evaluating the preventive effect of tetracycline on afatinib induced-skin toxicities in non-small cell lung cancer patients. Lung Cancer 2015;88:282-8.
15. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:213-22.
16. Yang JC, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3342-50.
17. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
18. Jatoi A, Dakhil SR, Sloan JA, et al. Prophylactic tetracycline does not diminish the severity of epidermal growth factor receptor (EGFR) inhibitor-induced rash: results from the North Central Cancer Treatment Group (Supplementary N03CB). Support Care Cancer 2011;19:1601-7.
19. Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-Emptive Skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol 2010;28:1351-7.
20. Lacouture ME, Keefe DM, Sonis S, et al. A phase II study (ARCHER 1042) to evaluate prophylactic treatment of dacomitinib-induced dermatologic and gastrointestinal adverse events in advanced non-small-cell lung cancer. Ann Oncol 2016. [Epub ahead of print].
21. Janjigian YY, Groen HJ, Horn L, et al. Activity and tolerability of afatinib (BIBW 2992) and cetuximab in NSCLC patients with acquired resistance to erlotinib or gefitinib. J Clin Oncol 2011;29:abstr 7525^.
22. Scope A, Agero AL, Dusza SW, et al. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. J Clin Oncol 2007;25:5390-6.
23. Lacouture ME, Schadendorf D, Chu CY, et al. Dermatologic adverse events associated with afatinib: an oral ErbB family blocker. Expert Rev Anticancer Ther 2013;13:721-8.

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