# 2022 Targeted Therapies Patient Forum

# Dermatologic Side Effects of EGFR-TKIs

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**TRANSCRIPT**

As Dr. Hirsch and Dr. Florez wonderfully discussed the advances that have been made in the past several decades in terms of understanding biology and then advancing the therapeutic landscape of lung cancer. It's also becoming very important to understand and recognize some of the side effects associated with targeted therapies for lung cancer for safe and effective therapy.

So, there are about 21 unique agents that are approved by the FDA for the treatment of non-small cell lung cancer. In my talk, I'm going to focus on EGFR, ALK, and ROS1 genomic alterations, given the time. However, some of the principles and suggestions can be applied to the side effects that arise in the setting of other targeted therapy drugs.

EGFR is a molecule that is widely expressed throughout our body. So, it's not surprising to see that various organ systems are affected by EGFR inhibitors. Here, I'm going to focus on skin and GI side effects, as well as some of the rare but important to recognize side effects, like the pulmonary and heart side effects.

When EGFR is inhibited in the skin, several changes happen. First, there's an alteration in the chemokine expression in the skin, leading to the recruitment of some of the innate and adaptive immune cells, such as macrophages, dendritic cells, and T cells. This is followed by an alteration in the differentiation of the epidermis, which is the upper part of the skin, and also a change in the expression of antimicrobial defense genes in the keratinocytes. A combination of these factors leads to the development of skin toxicity in the setting of EGFR inhibitors.

This is a general timeline of skin side effects that develop with EGFR Tyrosine Kinase Inhibitor therapy. First, we see rash and itching develop, followed by dry skin, skin fissures, stomatitis (which is oral cavity inflammation), and sores. Nail changes follow thereafter.

As Dr. Hirsch mentioned, there are three generations of EGFR Tyrosine Kinase Inhibitors: first, second, and third. Based on the FLAURA trial and others, we utilize third-generation treatment more often than the earlier-generation inhibitors. With a third-generation EGFR inhibitor, such as osimertinib, the incidence of rash is less compared with first and second-generation drugs, and it ranges from 40% to 50%. It is rare to see a high-grade (grade 3 or higher) rash with the third generation of EGFR inhibitor therapy. The itching and dry skin are seen across all the EGFR Tyrosine Kinase Inhibitors.

In terms of paronychia, which is a term to describe inflammation or infection around a finger or toenail, happens across generations of drugs. However, it occurs perhaps more commonly with the second generation. In terms of third-generation inhibitor therapy, the range of paronychia incidence is from 20% to 30%. But again, it is rare to see a high-grade paronychia with the use of third-generation inhibitors.

I'm showing you some pictures that really exemplify the acneiform rash, the acne-like rash that happens with EGFR inhibitor therapy. The picture on the left is a patient who is taking first-generation EGFR TKI therapy, and you see that there are sort of pimples on the face, and then puss-feeling lesions as well, that are tiny. On the right is a patient who is taking osimertinib, which is a third-generation EGFR Tyrosine Kinase Inhibitor, showing a lesser degree of rash, as you can see.

And how do we manage acneiform rash? This rash can have a substantial impact due to its appearance, and sometimes the itching associated with it can cause pain. When the rash is mild or grade one defined by less than 10% body surface area involved, we think about using topical corticosteroids. For the face and neck, we consider using low-potency steroids such as hydrocortisone or moderate-potency steroids such as triamcinolone. For the body or the trunk, we can increase the potency of steroids, such as Clobetasol cream, which is considered a high-potency steroid cream. This can be supplemented by topical antibiotics such as Clindamycin 1% gel. When the rash is mild and grade one, we usually continue the EGFR therapy.

When the rash becomes moderate, or grade two, defined by 10% to 30% body surface area involved, we still use topical corticosteroids. Then we consider using oral tetracycline antibiotics such as Doxycycline and Minocycline. In my clinic, I assess patients frequently, every two weeks or so, to determine how long the patient may need to stay on their oral antibiotics. Unless the rash is intolerable, there is usually no need to interrupt the therapy.

When the rash is severe, or grade three, defined by more than 30% body surface area involved, we use topical steroids and oral antibiotics, but that consideration can also be given to a short course of oral corticosteroids so that the steroids can be distributed throughout the body. For example, we can use Prednisone 0.5 to 1.0 mg per kg for a few days. In this setting, we think about holding the therapy. If there are lesions that have pus or other discharge, cultures can be sent for further workup.

As I mentioned, EGFR Tyrosine Kinase Inhibitor Therapy can cause xerosis, which is dry, and sometimes scaly, skin as you can see in the picture. This can be accompanied by itching.

When the itching is localized, we can utilize topical steroids. But if the itching is more generalized, we can think about using oral antihistamines such as Hydroxyzine, Gabapentin, or Pregabalin, which are GABA agonists. For the prevention and treatment of dry skin, we recommend using moisturizing creams regularly or lotions without any irritants such as fragrances or alcohol. For scaly dry skin, as seen in the previous picture, exfoliants such as Ammonium Lactate or Urea can be utilized.

So, paronychia can be a very challenging side effect of EGFR Tyrosine Kinase Inhibitor therapy. The pictures at the top really show the severe cases of paronychia. You see a red and inflamed paronychia around the toe and fingernails. At the bottom, you see mild cases of paronychia. Nail changes can happen, as I mentioned, and these include nail discoloration and a brittle nail.

So, it is important to minimize the trauma around the finger or toenail. Therefore, we recommend wearing comfortable shoes and wearing gloves when doing house chores or dishes, essentially any tasks using hands. Also, it's important to avoid biting nails and cutting them too short. When there is a concern about an ingrown toenail that may cause trouble down the road, getting a preventive correction procedure may be reasonable. Additionally, it's important to apply emollients, such as moisturizing creams around the nails, so that the area is continuously moisturized to prevent the development of paronychia.

The management of paronychia is quite similar to the rash that I discussed previously. When it's mild, defined by no pain, no discharge, or no nail plate separation, we can use topical steroids or antibiotics or antiseptics. If it's associated with pain or discharge, then we use these topical creams and products, but also oral antibiotics such as tetracycline antibiotics can be considered. If it's severe, causing severe pain, discharge, and infection, we need to think about interrupting the EGFR TKI therapy and utilizing the topical products and oral antibiotics. At this point, I would consider referring patients to a specialist for further evaluation.