Management Approaches for EGFR Inhibitor-Induced Rash

After describing the association of a rash on EGFR inhibitors with overall better outcomes on this class of agents, we can now take a step back and recognize that the rash can be an annoyance at the very least and sometimes a real problem. While there are no established guidelines, both treating physicians and patients have developed experience with the rash over the past few years that we should be able to use to minimize the impact for the majority of patients and reduce the proportion of people who need stop a potentially helpful agent due to this toxicity.

First, we need to clarify that multiple types of EGFR inhibitors can induce skin toxicities. Although Iressa and Tarceva, oral small molecules that block the “tyrosine kinase” signalling of the receptor, have been the best studied of these, monoclonal antibodies against EGFR, such as erbitux/cetuximab and others that are less well studied in lung cancer also produce skin toxicities. And while we generally think of this as a “rash”, other skin symptoms such as dry skin and itching are very common and are in the same category as a visible rash. And while it is most commonly the skin and particularly the face, neck, and trunk that are affected, other parts of the body can be affected. Eyes (leading to dry eyes/irritation), mouth, nose, and other mucosal surfaces can also be involved.

Second, we need to define the grading system. Technically, there is a formal scale for defining rash. Grade 1 is flat spots (macules) or raised spots (papules) or skin redness not associated with other symptoms. Grade 2 is the same kind of rash, covering less than 50% of the body surface and associated with itching or other symptoms. Grade 3 would be a symptomatic generalized rash over more than half of the body surface or whole body redness (“eythroderma” – not necessarily a rash of spots, but the skin uniformly red and thicker than usual). And grade 4 is with ulcerations and is fortunately quite rare with these agents. Most of these rashes are grade 1 or 2, but some are grade 3. That said, many times in clinical practice we just consider a rash as mild, moderate, or severe. A small patch of pimples around the nose that are itchy would be considered grade 2 by the toxicity grading system, but the patient and the doctor would often just consider this mild.

OK, so why do EGFR inhibitors cause a rash and/or other skin side effects? Well, EGFR stands for Epidermal Growth Factor Receptor, and this molecule is on the skin and hair follicles. EGFR plays a role in the normal development (or differentiation) and functioning of these, and EGFR inhibitors can block that and lead to occlusion of skin follicles. And EGFR inhibitors can lead the sebaceous glands connected to hair follicles to increase production of inflammatory mediators. So, to summarize the cause, we don’t really know.

What can be done? One of the issues is to ensure that patients take oral EGFR inhibitors like Tarceva at roughly the same time of day, and very importantly, on an empty stomach, as in at least one hour before or two hours after eating. That is important because the blood levels after taking tarceva, for instance, on an empty stomach are much more predictable than taking it with food. The studies used tarceva on an empty stomach because they previously found that the blood levels were often higher but very unpredictably so after taking it with food.
One of my friends and colleagues, Dr. Ed Kim at MD Anderson Cancer Center in Houston, has generated some summary concepts and ideas. Here’s a slide/figure based on his key points:

![Rash Management: A Potential Approach](image)

(click to enlarge)

What are those key points? Be proactive in dealing with problems before they become major issues. As the slide suggests, I give my patients prescriptions for clindamycin (an antibiotic, also known as Cleocin) gel, and also topical hydrocortisone 1% cream (also available over the counter), along with the prescription for tarceva. I advise to use these early if a rash appears. I also advise patients to avoid significant sun exposure. Then I have patients return to the clinic two weeks after starting tarceva, to check how they’re feeling, to check labs, and primarily to ensure that patients are not experiencing a terrible rash. For more significant rashes (grade 2 or higher), we often give oral antibiotics such as minocycline, and oral steroids. Some people distinguish between a flat rash and a bumpy, angrier one, and use steroids preferentially for flat rashes and antibiotics for pustules. Another approach that has recently been described uses a combination of an antibiotic like minocycline and the prescription non-steroidal topical cream for eczema called Elidel (1%). I haven’t had a patient who needed this since learning about this, but I’ve heard other doctors describe very good results with it in their experience for EGFR-induced rashes.

The rash tends to be worst after about 2-3 weeks and then tends not to get worse and often gets a bit better over time. I have seen several patients who develop more skin side effects later, but that’s not the typical scenario.

For dry skin and itching, we recommend emollients. Vaseline intensive care may do the job. There’s also lotions like “Lac-Hydrin” (Lactic Acid 12%) that can effectively help. For generalized itching, I give antihistamines like atarax or benadryl, which seem to help some.

The consensus from the people who have really been concentrating on this is that it isn’t acne and should be treated with over-the-counter acne medications or prescription acne medications like Accutane (isotretinoin).

Even with these interventions, sometimes the rash is severe enough to need to take a break or cut the dose. Stopping treatment temporarily will generally lead to a rapid improvement in skin symptoms, usually in just a few days. A significant minority of patients will need to decrease the dose of Tarceva to 100 mg, or sometimes lower than that. Tarceva tablets come not only in the 150 mg dose, but also 100 mg and 25 mg tabs, so it’s possible to cut down to 100 mg or lower if needed. Clearly, some patients are very sensitive to these agents, and we have NOT seen any evidence that patients who need to take a lower dose because of severe rash or...
other side effects do less well than the patients who took 150 mg. If anything, we see that the patients who developed a significant rash at some point (some of whom would have received subsequent dose reductions) did particularly well.

There are plenty of other issues, like hair changes of all types, and breaks in the skin or infections at the tips of the fingers and toes, that can also be seen. Most of these don’t have any standard approaches, but I’d love to learn if people have found helpful. I learn from the experiences of other docs and also patients and will be eager to try to aggregate our knowledge to make this type of therapy as easy to tolerate as possible.