# Dermatological Toxicity from Epidermal Growth Factor Receptor Inhibitors (EGFRI)

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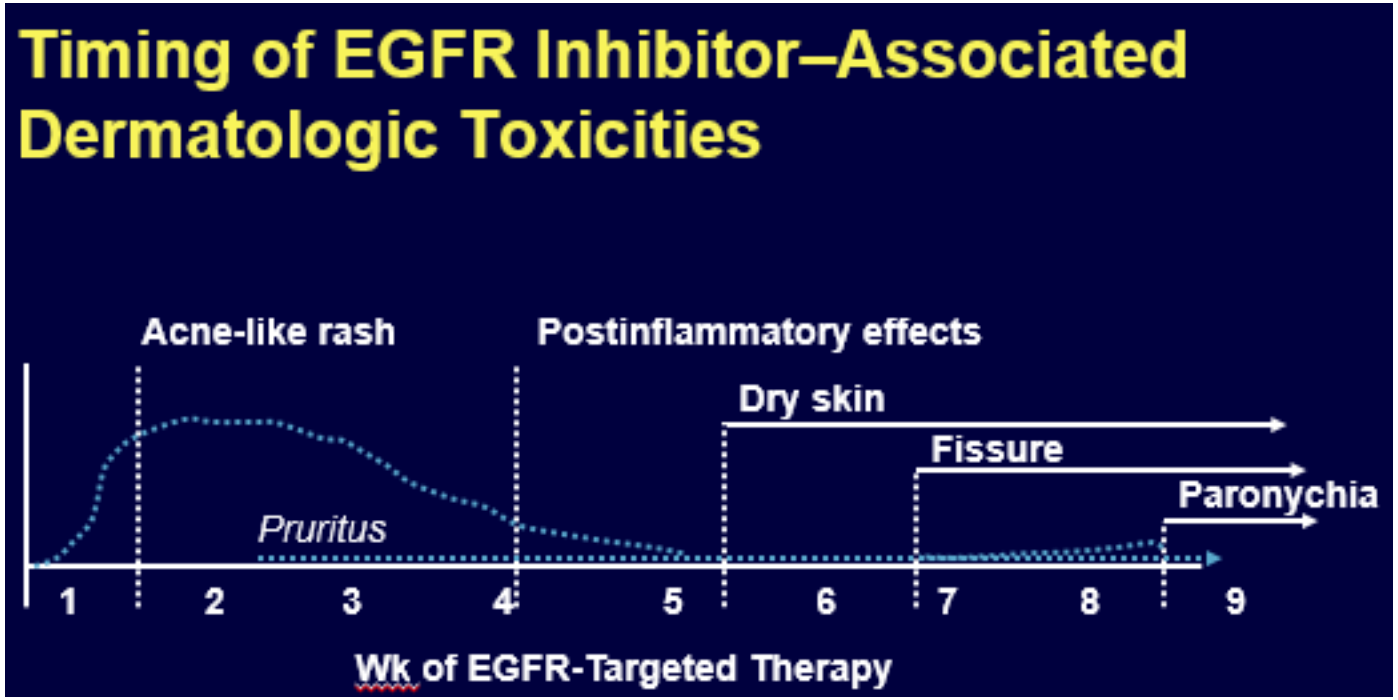
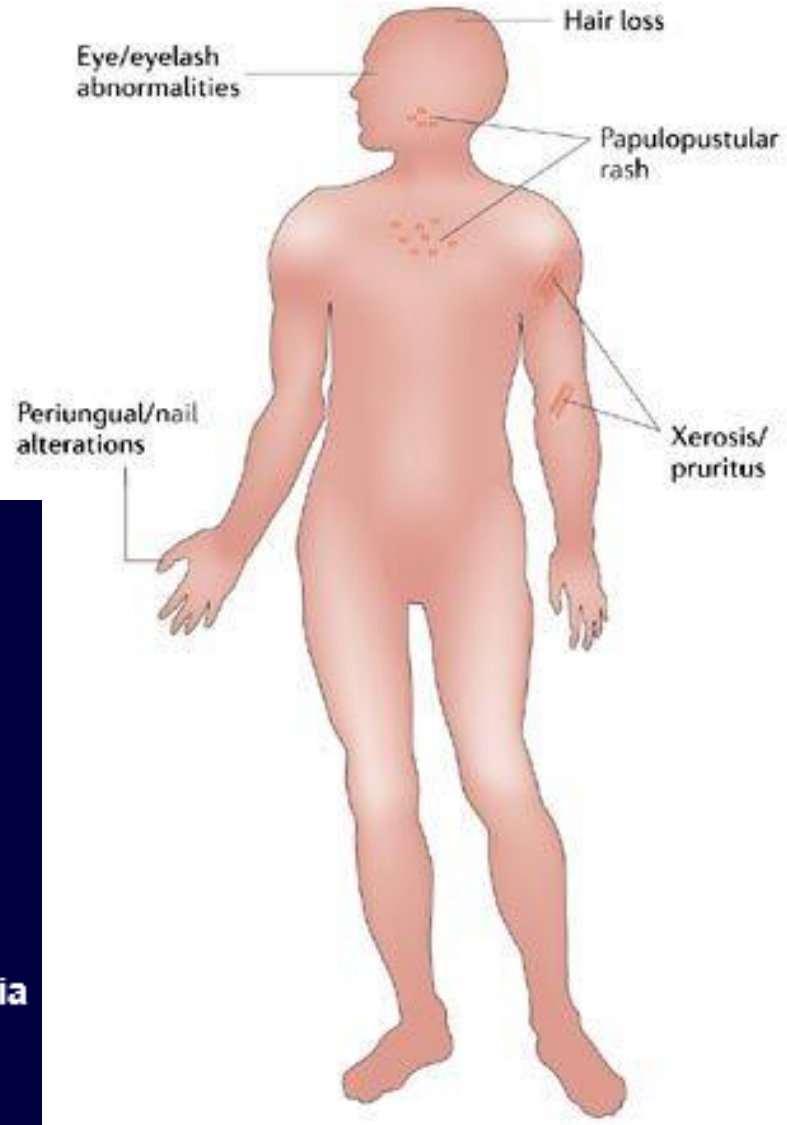
# Learning Objectives

- Prophylaxis and treatment of dermatological toxicities associated with EGFR inhibitors
- Counselling of patients on the anticipated dermatologic toxicities associated with EGFR inhibitors

# Introduction



# How to prevent or treat these dermatological toxicities?

# MASCC Guideline in Prevention and Treatment

## Levels of Evidence

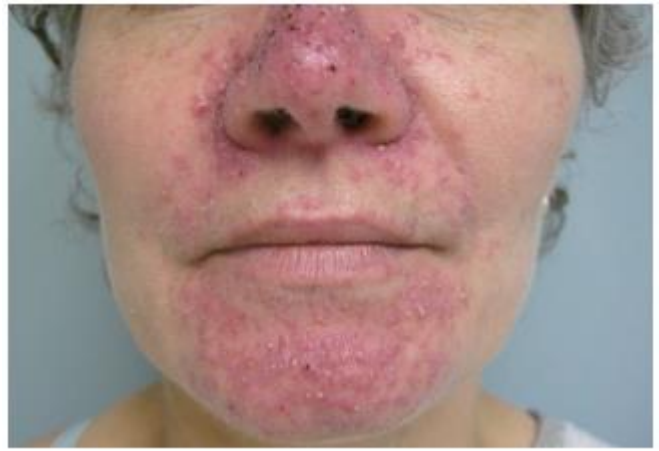
- Level I evidence is reserved for meta-analyses of randomized controlled trials or randomized trials with high power
- Level II evidence includes randomized trials with lower power
- Level III evidence includes nonrandomized trials, such as cohort or case-controlled series
- Level IV evidence includes descriptive and case studies
- Level V evidence includes case reports and clinical examples

## Recommendation Grades

- Grade A is reserved for level I evidence or consistent findings from multiples studies of level II, III, or IV evidence
- Grade B is for level II, III, or IV evidence with generally consistent findings
- Grade C is similar to grade B but with inconsistencies
- Grade D implies little or no evidence

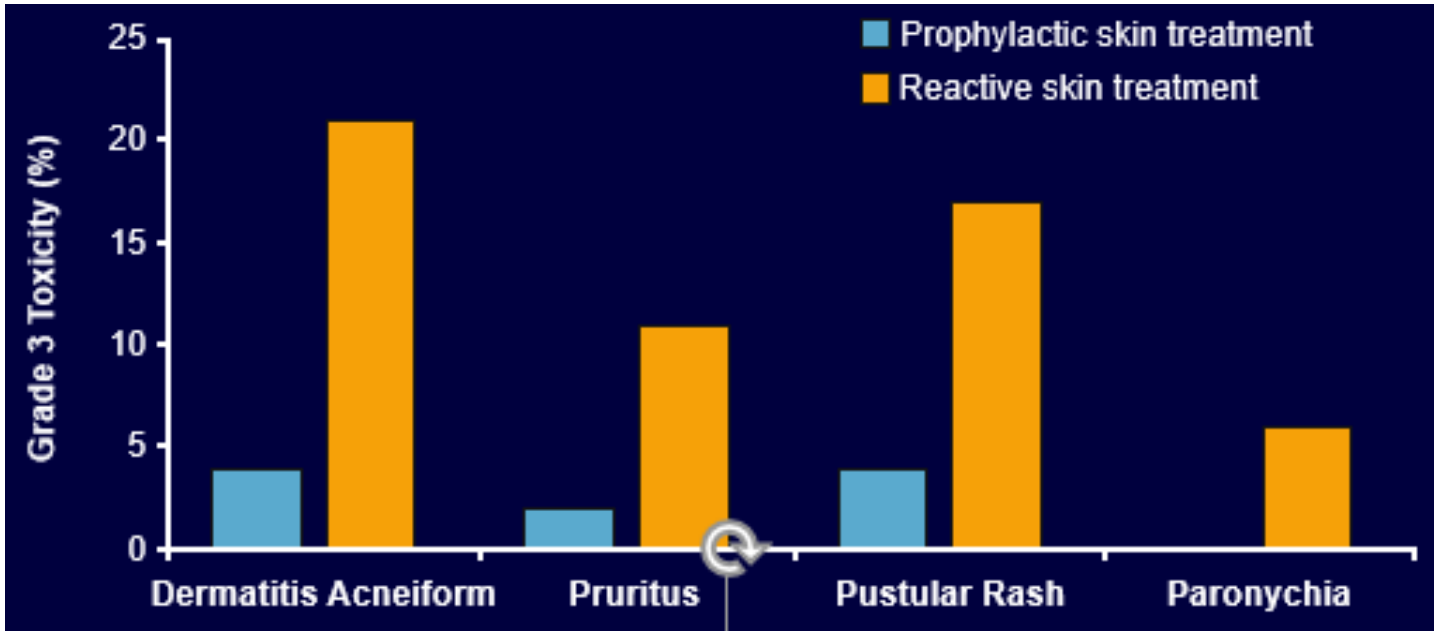
# 1. Papulopustular (Acneiform) Rash

- Most common (43-85%)
- Occur during the first weeks to months of EGFR inhibitor (EGFRI) therapy
  - Present 7-10 days after drug initiation
  - More common with monoclonal antibodies than tyrosine kinase inhibitors
- Affects mainly the head, neck and upper trunk
- Different from traditional acne
  - Lack of comedones
  - Often display crusting and confluence
  - Pruritis more common
- Associated with treatment efficacy: ↑OS
- Effects are dose dependent
- Improvement can be seen within 1-2 weeks of therapy discontinuation



# STEPP Study

- Open-label phase II study
- Preemptive vs reactive skin toxicity treatment for patients receiving panitumumab in met CRC




Prophylactic skin treatment starting on day 1 to week 6

- Skin moisturizer
- Sunscreen (PABA free, SPF ≥ 15, UVA/UVB protection)
- Topical steroid (1% hydrocortisone cream)
- Doxycycline 100 mg BID

Reactive treatment administered anytime during the 6 weeks

# Prophylaxis

| | Recommend | Not recommended | Level of evidence | Recommendation grades | Comments |
|---|---|---|---|---|---|
| Preventive (weeks 1–6 and 8 of EGFRI initiation) | | | | | |
| Topical | Hydrocortisone 1% cream with moisturizer and sunscreen twice daily | Pimecrolimus 1% cream<br>Tazarotene 0.05% cream<br>Sunscreen as single agent | II[a] | C | |
| Systemic | Minocycline 100 mg daily<br>Doxycycline 100 mg bid | Tetracycline 500 mg bid | II[a] | A | Doxycycline is preferred in patients with renal impairment. Minocycline is less photosensitizing. |

- Postinflammatory skin alterations (erythema and hyperpigmentation) can last for months or years
  - Continue prophylaxis to minimize these late effects.

# Treatment

| | Recommend | Not recommended | Level of evidence | Recommendation grades | Comments |
|---|---|---|---|---|---|
| Treatment | | | | | |
| Topical | Alclometasone 0.05% cream<br>Fluocinonide 0.05% cream bid<br>Clindamycin 1% | Vitamin K1 cream | IV[a] | C | |
| Systemic | Doxycycline 100 mg bid<br>Minocycline 100 mg daily<br>Isotretinoin at low doses (20–30 mg/day) | Acitretin | IV[a] | C | Photosensitizing agents |

[a] EGFRI study

- Focus more on reducing inflammation
  - Medium- to high-potency topical corticosteroids
  - If severe, can consider short course of systemic corticosteroids
  - EGFRI dose reduction/interrruption

# Management of Pruritus

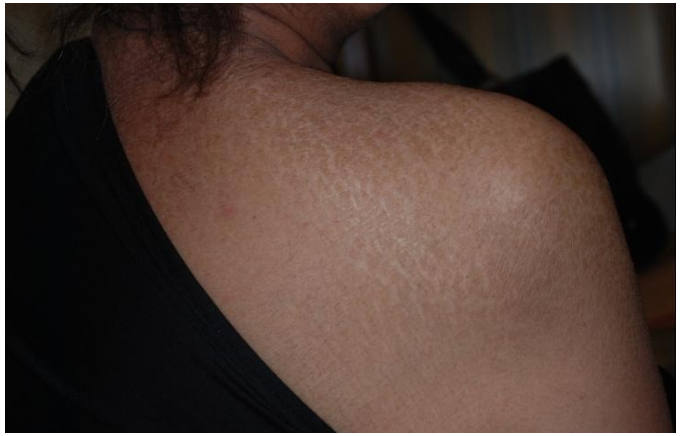
| | Recommend | Not recommended | Level of evidence | Recommendation grades | Comments |
|---|---|---|---|---|---|
| Preventive | | | | | |
| Topical | Gentle skin care instructions | | IV[a, b] | D | Consensus of experts |
| Systemic | | Steroids | IV[a, b] | D | Consensus of experts |
| Treatment | | | | | |
| Topical | Menthol 0.5%–pramoxine 1%–doxepin<br>Medium- to high-potency steroids (triamcinolone acetonide 0.025%; desonide 0.05%; fluticasone proprionate 0.05%; alclometasone 0.05%) | | III[b] | B | Treat underlying condition first (rash, xerosis) |
| Topical | | Antihistamines<br>Lidocaine | II[b] | C | These agents can become allergens, and can be absorbed systemically |
| Systemic | Antihistamines[b] | | I[c] | A | Nonsedating first; some may need adjustment for renal impairment |
| Systemic | | Aprepitant[a] | V[a] | D | |
| Systemic | Gabapentin/pregabalin[a] | | V[b,a] | D | Recommended as second-line treatment only if antihistamines fail |
| Systemic | Doxepin | | V[a] | D | |

[a] EGFRI study

[b] Non-EGFRI noncancer treatment study

[c] Non-EGFRI cancer treatment study

# 2. Xerosis



- Aka dry skin
- Late onset (~1-2 months after initiation of therapy)
  - Often accompanies or succeeds papulopustular rash
- Can turn into xerotic dermatitis (inflammation resulting from dry skin)
- If significant, can form skin fissures and deep cracks in the skin
  - Usually in the fingertips, in the palms/knuckes or soles
  - Painful
  - Risk of infection

| | Recommend | Not recommended | Level of evidence | Recommendation grades | Comments |
|---|---|---|---|---|---|
| Preventive | | | | | |
| Topical | Bathing techniques using bath oils or mild moisturizing soaps and bathing in tepid water<br>Regular moisturizing creams | | III | B | |
| Other | Avoid extreme temperatures and direct sunlight | | III[a] | B | |
| Treatment | | | | | |
| Topical (mild/ moderate) | Emollient creams that are packaged in a jar/tub that lack fragrances or potential irritants | Alcohol-containing lotions | III | B | More greasy creams for use on the limbs, but caution use of greasy creams on the face and chest |
| | Occlusive emollients containing urea, colloidal oatmeal, and petroleum-based creams<br>For scaly areas, use exfoliants: ammonium lactate 12% or lactic acid cream 12%<br>Urea creams (10–40%)<br>Salicylic acid 6%<br>Zinc oxide (13–40%) | Retinoids or benzoyl peroxide | | | Exfoliants may sting or burn when applied to eroded or erythematous skin—apply only on intact skin |
| Topical (severe) | Medium- to high-potency steroid creams (triamcinolone acetonide 0.025%; desonide 0.05%; fluticasone proprionate 0.05%; alclometasone 0.05%) | | III | B | |

[a] EGFRI study

# Management

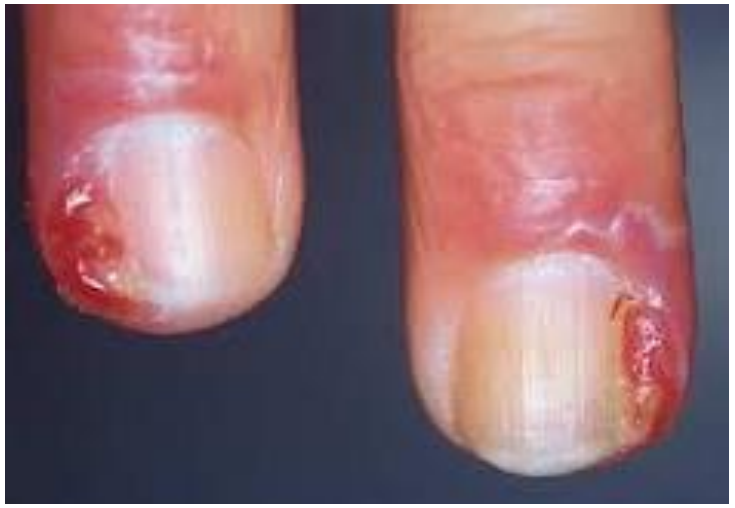
- If skin fissures occur

| | Recommend | Not recommended | Level of evidence | Recommendation grades | Comments |
|---|---|---|---|---|---|
| Preventive | | | | | |
| Topical | Wear protective footwear and avoid friction with fingertips, toes, and heals | | III | B | |
| Treatment | | | | | |
| Topical | Thick moisturizers or zinc oxide (13–40%) creams<br>Liquid glues or cyanoacrylate to seal cracks<br>Steroids or steroid tape, hydrocolloid dressings, topical antibiotics<br>Bleach soaks to prevent infection<br>Zinc oxide | | III[a]/[b] | B | Cream application often impractical |

[a] EGFRI study

[b] Non-EGFRI cancer treatment study

# 3. Paronychia



- Seen in up to 17% of patients
- Occur > 2 months after therapy initiation
- Present with painful inflammation and suppuration of the nail folds
  - Can bleed easily
  - Usually lesions are sterile
  - Secondary infection can occur
- Increased local trauma believed to be an aggravating factor

| | Recommend | Not recommended | Level of evidence | Recommendation grades | Comments |
|---|---|---|---|---|---|
| Preventive | | | | | |
| Topical | Diluted bleach soaks<br>Avoid irritants | | II[a] | A | Recommend final concentration of approximately 0.005% (approximately 1/4–1/8 cup of 6% bleach for 3–5 gal water) |
| Treatment | | | | | |
| Topical | Corticosteroids<br>Calcineurin inhibitors | Antifungals<br>Antibiotics | II[a] | A | Recommend usage of ultrapotent topical steroids as first-line therapy given cost and availability of these agents |
| Systemic | Tetracyclines | Empiric antibiotics—employed without culturing lesional skin | IV[b]/II[a] | D/A | |
| | Antimicrobials: reserved for culture proven infection | Antifungals | | | |
| Systemic | Biotin for brittle nails | | III[a] | B | |
| Other | Silver nitrate chemical cauterization weekly<br>Electrodessication<br>Nail avulsion | | IV[a] | D | Reserved for pyogenic granulomata; cnsensus of experts |

[a] Non-EGFRI noncancer treatment study

[b] EGFRI study

# Management

- Minimize trauma
  - Wear comfortable shoes
  - Avoid excessive manicuring
  - Wear gloves while doing household chores
- Decrease inflammation
  - Topical corticosteroid
  - Systemic tetracycline
- Prevent superinfection
  - Antimicrobial soaks (diluted bleach or vinegar)
- Eliminate excessive granulation tissue
  - Silver nitrate
  - Nail avulsion

** Obtain a culture, treat with antimicrobials as necessary **

# 4. Hair Changes

- Presentation:
  - First 1-2 months of therapy:
    - Trichomegaly (elongation and curling of eyelashes)
    - Hypertrichosis eg facial hirsutism
  - 2-3 months after initiation of therapy:
    - Scalp hair changes
      - Fine, brittle hair with frontal balding
      - Generally resolves after discontinuation of therapy, although hair regrowth may be of varying quality
      - With time, scarring alopecia can occur and lead to permanent hair loss

| | Recommend | Not recommended | Level of evidence | Recommendation grades | Comments |
|---|---|---|---|---|---|
| Preventive hair loss | | | | | |
| Topical | For scarring alopecia, follow rash recommendations | Preventive interventions for nonscarring alopecia | V | D | |
| Systemic | For scarring alopecia, follow rash recommendations | Preventive interventions for nonscarring alopecia | V | D | |
| Treatment hair loss | | | | | |
| Topical | Nonscarring<br>Minoxidil 2%, 5% bid<br>Scarring<br>Class 1 steroid lotion, shampoo, or foam<br>Antibiotic lotion | | I[a]/II/III/IV[b] | B/D | Consensus of experts |
| Preventive increased hair | | | | | |
| | Patient education and support | | IV | B | Consensus of experts |
| Treatment increased hair | | | | | |
| Facial hypertrichosis | Eflornithine<br>Lasers | Waxing, chemical depilatories | IV[b], II[a] | B | Consensus of experts |
| Eyelash trichomegaly | Eyelash trimmings regularly | | IV | B | |

[a] Non-EGFRI noncancer treatment study

[b] EGFRI study

# Patient Education

- Patients should be educated about these potential dermatological events before receiving EGFRIs
  - Counsel patients on what to look for
  - Encourage patients to use preventive measures
  - Over-the-counter management
  - Emphasize on correct administration method
    - Eg Erlotinib to take on empty stomach. Food increases drug bioavailability
- Critical to ensure anticipatory coping

MASCC™
Multinational Association Of Supportive Care In Cancer
www.mascc.org

# Caring for Your Skin, Hair and Nails when on "Targeted Therapies"

"Targeted therapies" are a name for epidermal growth factor receptor inhibitors (EGFRIs). These types of drugs work in a number of cancers. They work by blocking cell processes that cancer cells need to survive. They hit a very specific set of cells in your body which is why EGFRIs are called "Targeted Therapies". Names of the most commonly used EGFRIs are:

- Erlotinib (Tarceva®)
- Cetuximab (Erbitux®)
- Panitumumab (Vectibix®)
- Lapatinib (Tykerb®)

Unfortunately, like other cancer drugs, EGFRIs have side effects. The most common body part affected by these drugs is the skin. These include: an acne-like rash, dry skin, itching, nail changes and hair changes. Although side effects are often mild or moderate, on occasion, they can be severe. When side effects are severe, your doctor may need to stop treatment either for a short time or permanently. So, it is important to know about preventing and treating the skin side effects.

**This patient brochure has been adapted from a brochure of the Memorial Sloan-Kettering Cancer Center*

## What to LOOK for:

### Acne-Like Rash:
An acne-like rash often begins 1-2 weeks after starting the drug. It may continue for many weeks and then slowly improve. It may look like acne but it is not acne and it will not improve with anti-acne medicines. The rash occurs most often on the face, neck, chest and back. The rash may cause discomfort or itching. For most people, the rash is mild to moderate and will not affect daily life. For some people, the rash is more severe and may make the person self-conscious about the way they look.

### Dry Skin:
After a couple of months, you may notice that your skin looks dry and scaly. This may happen on your arms, legs or body. The dryness may be so severe that the skin on the fingertips and heels crack.

### Itching:
Itching may start in the first few months of taking the drug. It may occur on the scalp, body, arms and legs. It also may itch where you have a rash or the skin is dry.

### Nail Changes:
One of the later side effects of these drugs can be painful swelling and redness around the fingernails or toenails. Sometimes the nail area can become infected and require antibiotics.

### Hair Changes:
After you are on the drug for awhile (usually over four months), your hair may change. Sometimes you can lose patches of hair or have hair thinning. On the other hand, you may also notice hair growing in areas such as the face. Eyelashes and eyebrows may grow very long. Long curling eyelashes may bother you and affect your vision.

## What You Should Do to Prevent or Manage Side Effects:

### General:
- Tell your doctor or nurse as soon as you have any skin, hair or nail problems.
- Avoid being in the sun and use a sunscreen with an SPF of 30 or more.

*If skin problems become severe, you may be sent to see a skin doctor, called a dermatologist.*

### Rash:
- Your doctor may prescribe an antibiotic to try to prevent or treat the rash. Do not stop taking your drugs unless your doctor or nurse tells you to stop.
- Your doctor may prescribe special creams to put on the red, inflamed areas.
  Do not use acne drugs or creams on the rash.

### Dry Skin:
- For dry skin, use over-the-counter moisturizers (Vanicream®, Eucerin®, Aquaphor®). In general, use ointments or creams sold in tubs and avoid lotions.
- For very dry skin that is scaly and flakey, use over-the-counter Am-Lactin® cream.
- For cracks in the fingertips, use creams or ointments containing zinc oxide (Desitin® regular or maximum strength®).
- Cracks also may be treated with Super Glue® to prevent pain and allow healing.
  Your doctor may prescribe special creams to put on dry patches that hurt or itch.

### Hair Changes:
- Use electric razors to remove any new or increased hair growth. Avoid using a straight razor, waxing or chemicals.

### Itching:
- For itchy skin, use over-the-counter creams that contain menthol. (Sarna Ultra cream®)
- Over-the-counter anti-histamines pills also may reduce itching (Benadryl®, Claritin®, etc.).
- Your doctor may prescribe other drugs or creams to be applied or taken by mouth. In general, anti-itch tablets cause drowsiness, so you may want to take them only at night.
- For itching on the scalp, try Selsun Blue®, Neutrogena T-Gel® or your doctor may order special foams or shampoos.

### Nail Changes:
- For swelling and redness around finger or toenails, wear soft shoes and avoid extreme heat or cold or bumping them
- Your doctor may use a special chemical (silver nitrate) that is put on every week.
- If there is pain or redness, soak fingers or toes in a solution of white vinegar mixed in an equal amount of tap water.
- Your doctor may prescribe antibiotics if there is an infection.

### Mouth changes:
- If you have mouth sores eat soft, non-spicy foods. Your doctor may prescribe pain medicine especially if the pain affects eating.
- Good oral care is important. Be sure to brush and floss your teeth and see an oral health care provider before treatment and during treatment.

*If you have any questions or concerns, ask your doctor or nurse. You also may see a dermatologist who knows about these side effects.*

# References


- Lacouture ME, Anadkat MJ, Bensadoun RJ et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer. 2011; 19:1079-1095