Skin reaction with erbitux

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What are the common side effects from EGFR inhibitor treatments?

Fatigue

Diarrhea

Headaches

Hypersensitivity Reactions

Skin toxicities including rash

What is the incidence of skin rash?

The acneiform (papulopustular) eruption is the prototypical cutaneous adverse reaction to treatment with EGFR inhibitors.

It occurs in over 80 percent of patients and is more frequent in older patients and in patients with light skin phototypes

Risk factors;
age
gender
skin phototype I/II
UV exposure
No smoking
combination therapy with chemotherapy agents.

•in patients with metastatic colorectal cancer treated with cetuximab, age ≤70 and male sex are associated with a higher rate of grade 3 eruption.

Fitzpatrick skin phototypes

Skin type	Unexposed skin color	Reaction to sun exposure*
I	White	Always burns, never tans
II	White	Always burns, minimal tan
III	White to olive	Burns minimally, gradually tans
IV	Light brown	Burns minimally, tans well
V	Brown	Very rarely burns, tans profusely
VI	Dark brown to black	Never burns, tans deeply

Note: Slight variations on the definitions of the phototypes appear in the literature.

Relationship between rash and survival

metastatic colorectal cancer patients harboring wild-type *KRAS who developed moderate or severe rash when treated with panitumumab or cetuximab had a* signiffcantly prolonged overall survival, progression-free survival, and overall response rate

The eruption develops mainly in areas rich in sebaceous glands (eg, scalp, face, upper trunk) within the first two weeks of therapy .

Erythematous papules and pustules evolve to crusted lesions and eventually resolve leaving persistent erythema, telangiectasias, and skin dryness.

Bacterial super infection may occur.

PATHOGENESIS

1.Direct receptor inhibition
2. Inflammatory response
3. Role of microorganisms

Diagnosis;

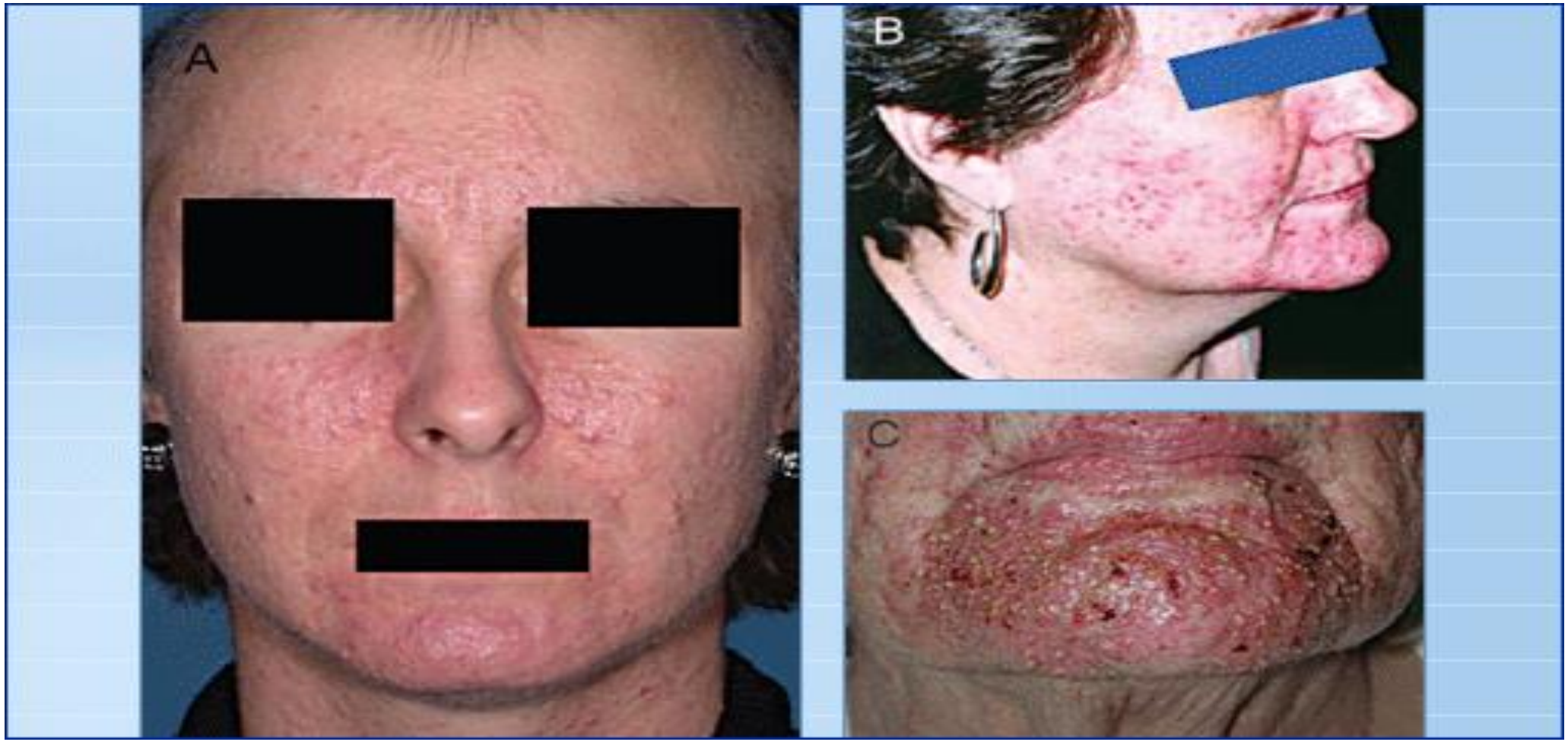
The diagnosis of acneiform eruption in patients receiving EGFR inhibitor therapy is usually straightforward, based upon the morphology and distribution of the skin lesions (eg, erythematous and follicular papules or pustules in areas rich in sebaceous glands with sparing of palmoplantar surfaces)

NCI CTCAE v5.0 acneiform rash

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acneiform rash	Papules and/or pustules covering <10% of the body surface area, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 to 30% of the body surface area, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL*; papules and/or pustules covering >30% of the body surface area, with or without mild symptoms	Papules and/or pustules covering >30% of the body surface area, which may or may with moderate or severe symptoms; limiting self-care ADL*; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any percent of the body surface area, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with intravenous antibiotics indicated	Death

An example of the course of rash:

from erythema to papulopustules



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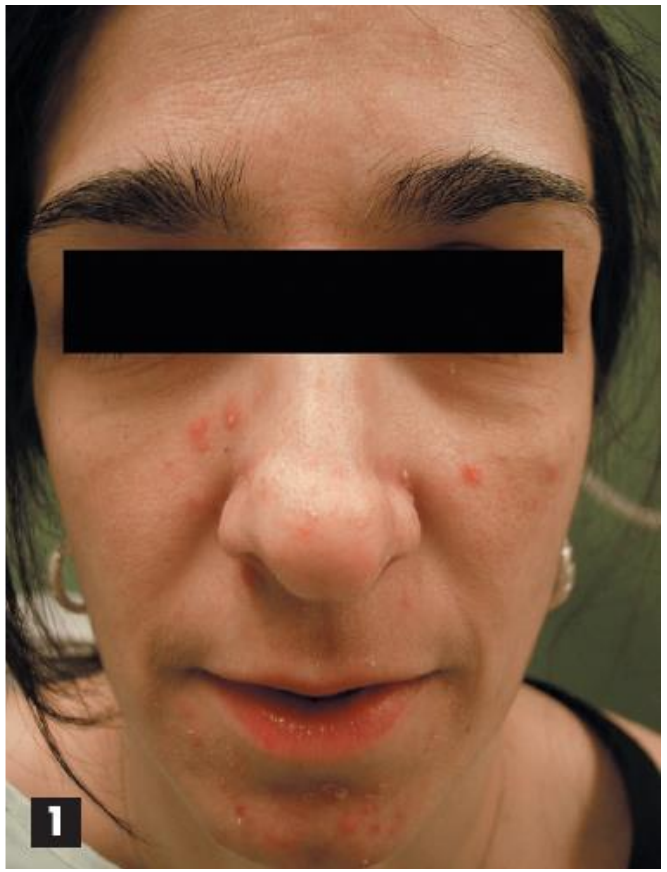
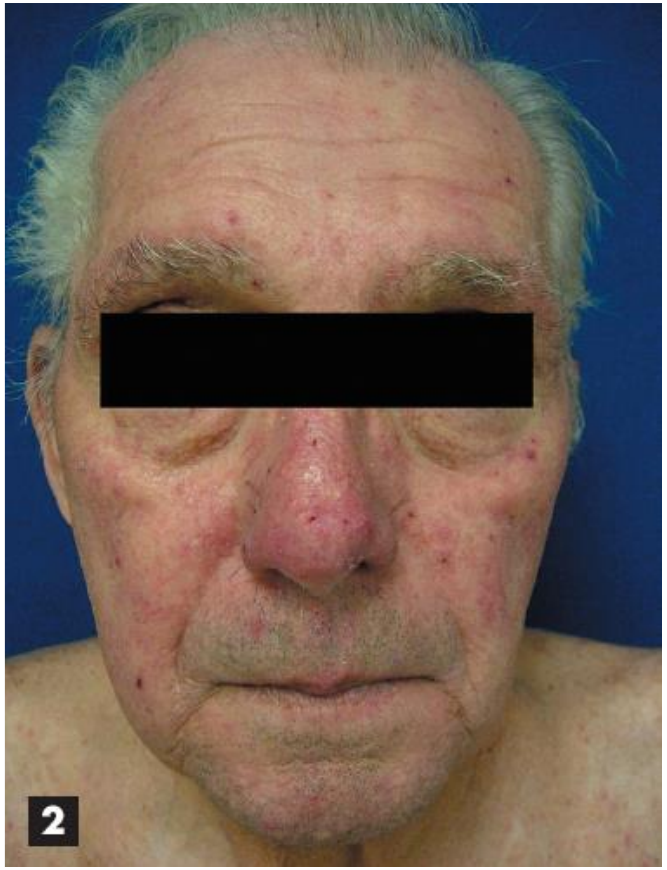
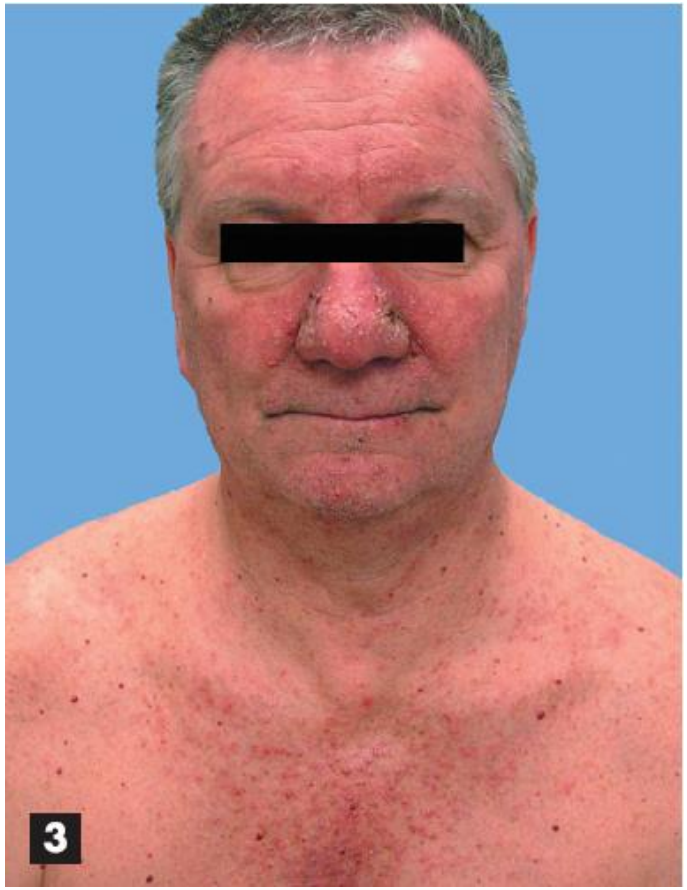


mild



moderate



severe

For patients with grade 1 rash ;

we suggest topical corticosteroids with or without topical antibiotics .

We use low potency topical corticosteroids (group six) twice a day for four weeks and clindamycin 1% gel twice a day for four weeks.

For patients with grade 2 rash ;

who are not taking prophylactic tetracyclines, we suggest topical corticosteroids and oral tetracycline antibiotics **.**

We use low potency topical corticosteroids (group six) twice a day for four weeks and either doxycycline 100 mg or minocycline 100 mg orally.twice a day for four weeks.

First-generation oral cephalosporins (eg, cephalexin, cefadroxil) or trimethoprim-sulfamethoxazole can be used as alternative antibiotics for patients who are taking prophylactic tetracyclines or do not benefit from tetracyclines.

For patients with grade ≥3 rash ;

In patients with grade ≥3 rash, intolerable grade 2 rash, or rash that interferes with self-care activities of daily living or impairs the quality of life , discontinuation or interruption of EGFR inhibitor therapy is warranted.

Treatment may be reinitiated after toxicity has resolved to baseline or less than or equal to grade 1, according to the instructions provided in the prescribing information for the particular agent.

In addition to discontinuation or interruption of EGFR inhibitor therapy, we suggest treatment with oral antibiotics plus a short course of systemic corticosteroids .

Oral doxycycline 100 mg or minocycline 100 mg is given twice a day for at least four weeks.

First-generation oral cephalosporins (eg, cephalexin 500 mg twice per day,cefadroxil 500 mg twice per day) or trimethoprim-sulfamethoxazole (trimethoprim 160 mg/sulfamethoxazole 800 mg/twice per day) given for four weeks can be used as alternatives when patients do not benefit from tetracycline antibiotics or have a culture-proven infection with organisms resistant to tetracycline antibiotics.

Oral prednisone 0.5 mg/kg up to a maximum of 40 mg per day is given for seven days.

Improvement should be noted within two weeks.

If a viral or bacterial superinfection is suspected, cultures of exudates should be obtained prior to the initiation of the antibiotic treatment to determine appropriate antimicrobial therapy.

Refractory grade ≥3 rash

— For patients with grade ≥3 rash that does not improve with the regimen of oral antibiotics plus systemic corticosteroids described above, low-dose isotretinoin (20 to 30 mg per day) or acitretin (25 mg a day) may be tried .

Oral tetracyclines are discontinued before initiating oral isotretinoin. Improvement is generally evident within four weeks.

Therapy is continued for at least two months after patients resume EGFR inhibitor at regular dose.

Improvement of pruritus and pain was also noted following initiation of oral retinoids.

Isotretinoin may aggravate some EGFR inhibitor adverse effects such as skin dryness, cheilitis, or photosensitivity.

If no improvement or worsening is noted despite dose modiffication, treatment with systemic antibiotics and systemic corticosteroids, or oral isotretinoin, interruption or discontinuation of EGFR inhibitor treatment may be necessary.

Treatment of EGFR inhibitor-induced acneiform rash

Severity (CTCAE v.4)	Intervention (reactive)*
Grade 0	Prophylactic therapy with sunscreen SPF ≥15; moisturizing creams; gentle skin care instructions given
Grade 1	Continue anticancer agent at current dose and monitor for change in severity ▪ Hydrocortisone 2.5% cream and clindamycin 1% gel Reassess after two weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve proceed to next step

Grade 2	Continue anticancer agent at current dose and monitor for change in severity ▪ Hydrocortisone 2.5%, desonide, alclometasone 0.05% creams to the face and neck or fluocinonide 0.05% cream to chest and back **AND** ▪ Doxycycline 100 mg **OR** minocycline 100 mg twice daily Reassess after two weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve proceed to next step
Grade 3 or intolerable grade 2	Dose modify as per PI; obtain bacterial/viral cultures if infection is suspected and continue treatment of skin reaction with the following ▪ Hydrocortisone 2.5%, desonide, alclometasone 0.05% creams to the face and neck or fluocinonide 0.05% cream to chest and back **AND** ▪ Doxycycline 100 mg **OR** minocycline 100 mg twice daily **AND** prednisone 0.5 mg/kg for seven days ▪ Consider low doses of isotretinoin (20 to 30 mg/day) Reassess after two weeks; if reactions worsen or do not improve, dose interruption or discontinuation per PI may be necessary

Dose modification guidelines for cetuximab based upon cutaneous adverse reaction

Severe acneiform rash	Initial management	Outcome	Dose modification
First occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m^2
		No improvement	Discontinue cetuximab
Second occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m^2
		No improvement	Discontinue cetuximab
Third occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m^2
		No improvement	Discontinue cetuximab
Fourth occurrence	Discontinue cetuximab		

PREVENTION

General measures

Before initiating treatment with EGFR inhibitors, patients should be educated about adopting general skin care measures, which include :

●Regularly using a broad-spectrum (UVA/UVB) sunscreen with SPF ≥15 with inorganic ingredients (zinc oxide, titanium dioxide)

- Limiting excessive sun exposure
- Using thick, alcohol-free emollients twice daily
- Avoiding over the counter anti-acne medications and alcohol-based skin care products
- Reducing the frequency and duration of hot showers
- Using tepid/lukewarm water for bathing
- Avoiding antibacterial or perfumed soaps and detergents

Preemptive therapy

Prophylaxis;

We suggest prophylactic oral tetracyclines in conjunction with topical corticosteroids for patients initiating treatment with EGFR inhibitors .

started on the same day as EGFR inhibitor therapy.

We typically use doxycycline 100 mg twice a day or minocycline 100 mg daily for six to eight weeks; low-potency corticosteroids such as hydrocortisone 2.5% or alclometasone 0.05% cream are applied twice a day.

Prophylactic treatments for skin reactions

Oral antibiotics

- Consider prophylactic use of oral tetracyclines for 6–8 weeks[1]

Topical corticosteroids

- Consider prophylactic use of topical hydrocortisone cream with moisturizer[2]