Management of skin toxicities in patients treated with anti-EGFR antibodies for metastatic colorectal cancer (mCRC)

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EGFR, epidermal growth factor receptor.

UK-ERB-00053 | February 2025

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Introduction

- Anti-EGFR inhibitors target pathways that are crucial for cancer cell growth and survival[1]
- Cetuximab is a monoclonal antibody (mAb) indicated for the treatment of patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer (mCRC):[2]
  - In combination with irinotecan-based chemotherapy
  - In first-line in combination with FOLFOX
  - As a single agent in patients who have failed oxaliplatin and irinotecan-based therapy and who are intolerant to irinotecan
- Panitumumab is an anti-EGFR mAb available for the treatment of EGFR-expressing, wild-type RAS mCRC:[3]
  - In first-line combination with FOLFOX or FOLFIRI
  - In second-line combination with FOLFIRI for patients who have received first-line fluoropyrimidine-base chemotherapy (excluding ironotecan)
  - As monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens
- Anti-EGFR specific side effects can result in decreased quality of life and interruption of treatment in some patients[1]
- Effective management is therefore recommended to aid patient compliance[4]

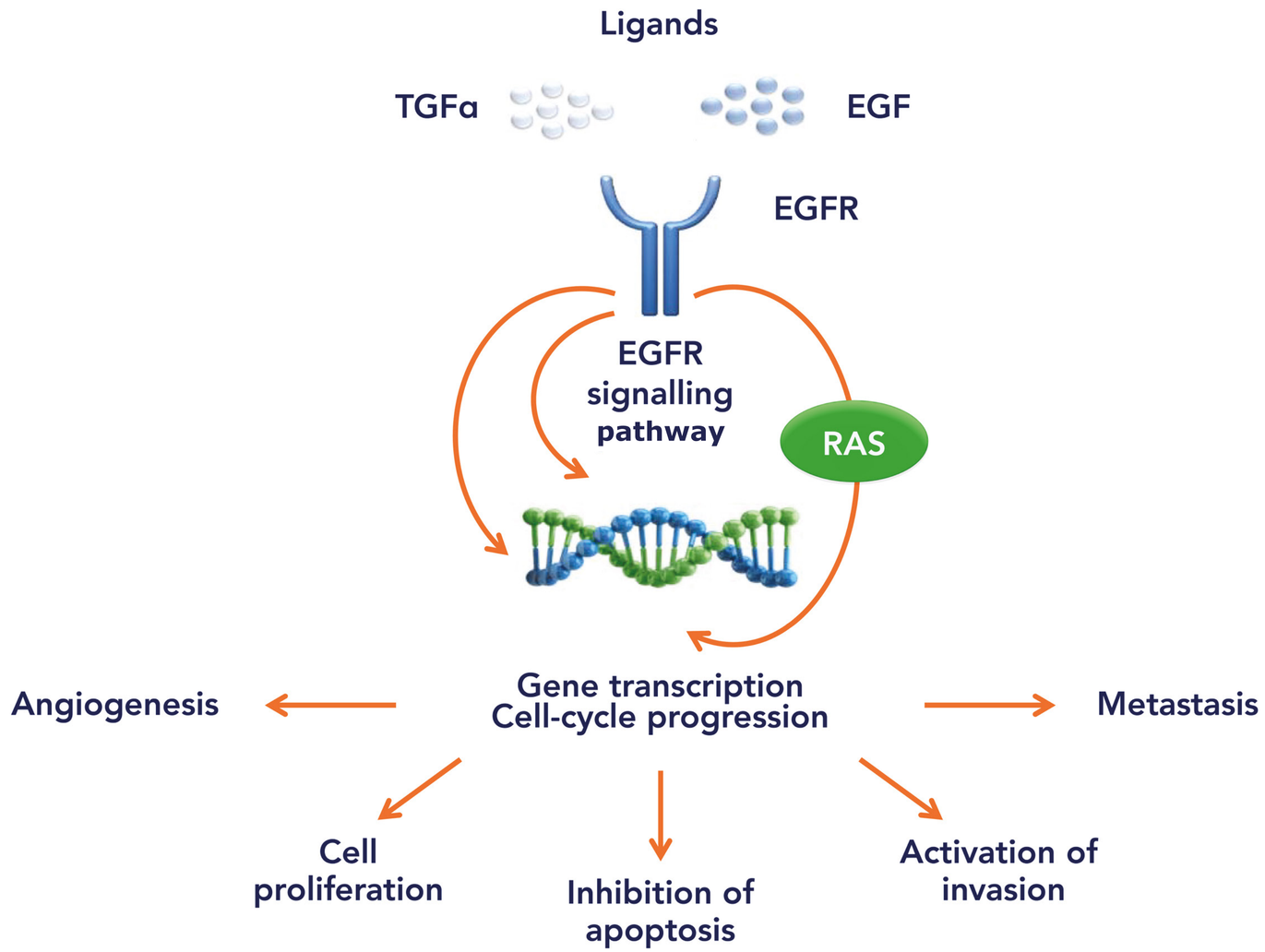
EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil, leucovorin and irinotecan; FOLFOX, fluorouracil, leucovorin and oxaliplatin; mAbs, monoclonal antibodies.

1. Lacoutre ME. *Nature Rev.* 2006;6:803-12; 2. Erbitux® SmPC. Merck; 3. Vectibix® SmPC. Amgen; 4. Segaert S, van Cutsem E. *Ann Oncol.* 2005;16:1425-33.

EGFR signalling pathway in mCRC

Activation of the EGFR signalling pathway in non-cancerous cells controls cell-cycle progression, differentiation and survival[1]

In cancerous cells, EGFR pathway activation results in cell proliferation, inhibition of apoptosis, activation of invasion, metastasis and angiogenesis[1-3]

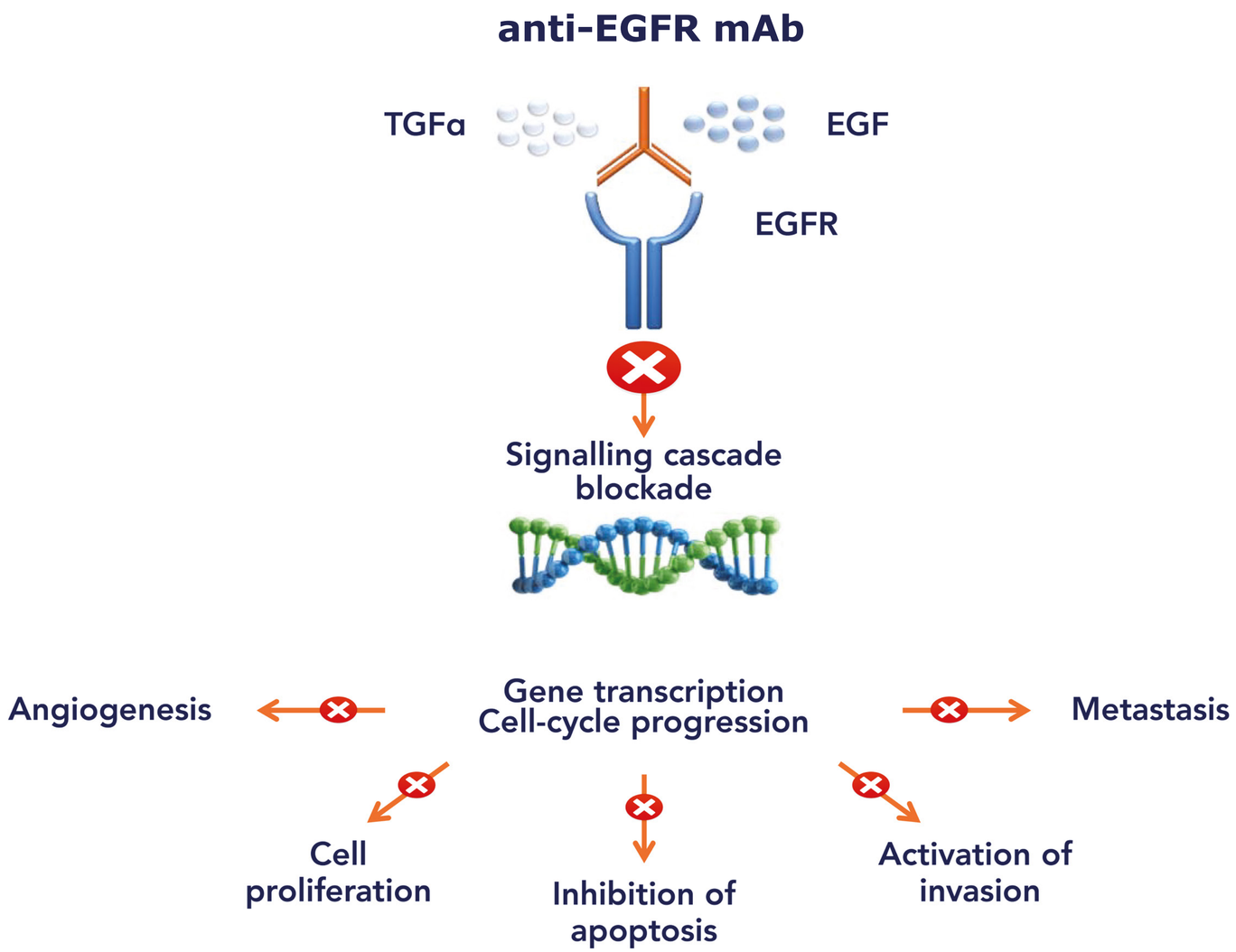


EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; TGF, transforming growth factor.

1. Ciardiello F, Tortora G. *Clin Cancer Res.* 2001;7:2958-70; 2. Ciardiello F, Tortora G. *N Engl J Med.* 2008;358:1160-74; 3. Cohen SJ, *et al. J Clin Oncol.* 2005;23:5374-85.

Mechanism of action of anti-EGFR mAbs in EGFR pathway

The anti-EGFR mAbs, cetuximab and panitumumab, block EGFR signal transduction and inhibit downstream intracellular signalling[1-4]



EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; mAbs, monoclonal antibodies; mCRC, metastatic colorectal cancer; TGF, transforming growth factor.

1. Bokemeyer C, *et al. J Clin Oncol.* 2009;27:663-71; 2. van Cutsem E, *et al. N Engl J Med.* 2009;360:1408-17; 3. Baselga J, *Eur J Cancer.* 2001;37:S16-22;
4. Benvenuti S, *et al. Cancer Res.* 2007;67:2643-8.

Role of EGFR in the skin

- EGFR is crucial for the normal development and physiology of the epidermis[1]
- Protects against UV-induced damage, inhibiting inflammation, and accelerating wound healing[1]
- Expressed in epidermal cells, sebaceous glands, hair follicles and the capillary system[2]

Impact of anti-EGFR inhibitors on the skin

- Dermatologic effects induced by EGFR inhibitors occur in sites where EGFR is expressed, for example:[2]
  - Epidermal cells
  - Sebaceous glands
  - Hair follicles
  - Capillary system

EGFR, epidermal growth factor receptor.

1. Lacoutre ME. *Nature Rev.* 2006;6:803-12; 2. Segaert S, van Cutsem E. *Ann Oncol.* 2005;16:1425-33.

Undesirable dermatological effects of anti-EGFR mAbs

Cetuximab

- Skin reactions occur in more than 80% of patients[1]
- Approximately 15% of the skin reactions are severe[1]

Panitumumab

- Skin reactions are experienced by nearly all (approximately 94%) patients[2]
- Approximately 23% of patients experience severe skin reactions[2]

If a patient experiences an intolerable or severe (grade ≥3; CTCAE) skin reaction to anti-EGFR mAb therapy, treatment must be interrupted[1,2]

Treatment may only be resumed if the reaction has resolved to grade 2 or lower[1,2]

CTCAE, Common Terminology Criteria for Adverse Events; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody.

1. Erbitux® SmPC. Merck; 2. Vectibix® SmPC. Amgen.

Dose interruption summary according to the Summary of Product Characteristics for cetuximab and panitumumab

Occurrence of grade ≥3 skin reaction	Cetuximab[1]		Panitumumab[2]	
	Administration	**On resolution to grade ≤2 skin reaction**	**Administration**	**If resolution to grade ≤2 skin reaction** (if not resolved - discontinue)
Initial occurrence	Interrupt treatment	Resume at previous dose (100%)	Interrupt 1 or 2 doses	Resume at 100% of original dose
Second occurrence	Interrupt treatment	Resume at a reduced dose (200 mg/m^2)	Interrupt 1 or 2 doses	Resume at 80% of original dose
Third occurrence	Interrupt treatment	Resume at a reduced dose (150 mg/m^2)	Interrupt 1 or 2 doses	Resume at 60% of original dose
Fourth occurence	Discontinue		Discontinue	

Grade of skin toxicity according to CTCAE (Common Terminology Criteria for Adverse Events).

1. Erbitux® SmPC. Merck; 2. Vectibix® SmPC. Amgen.

Main skin reactions with anti-EGFR mAbs listed in the Summary of Product Characteristics for cetuximab and panitumumab

Cetuximab[1]
Acneiform eruption
Pruritis
Dry Skin
Desquamation
Hypertrichosis
Nail changes (eg. paronychia)

Panitumumab[2]
Aceneiform dermatitis
Rash
Erythema
Pruritus
Dry skin
Skin fissures
Acne
Alopecia

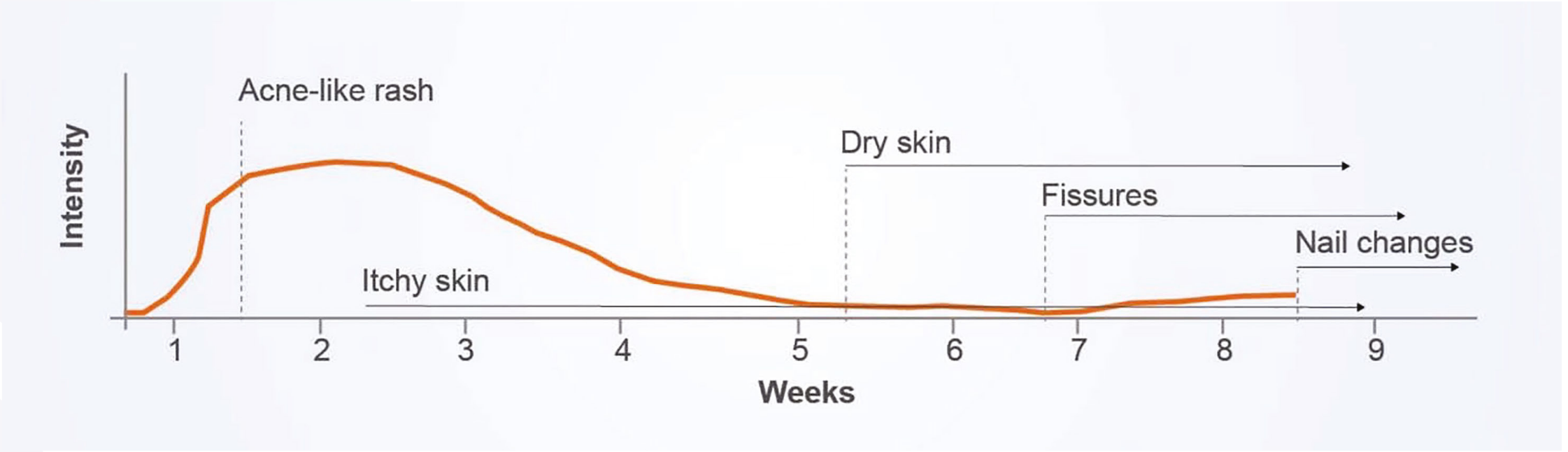
The majority of skin reactions for panitumamab develop within the first three weeks of therapy. They generally resolve, without sequelae, over time following cessation of treatment if the recommended adjustments in dose regimen are followed[2]

EGFR, epidermal growth factor receptor; mAbs, monoclonal antibodies.

1. Erbitux® SmPC. Merck; 2. Vectibix® SmPC. Amgen.

Timeline of skin reactions with anti-EGFR mAbs[1]

Skin reactions over time for both anti-EGFR mAbs



Adapted from van Cutsem E. *The Oncologist.* 2006[1]

EGFR, epidermal growth factor receptor; mAbs, monoclonal antibodies.

1. van Cutsem E. *The Oncologist.* 2006;11:1010-7.

Management of skin reactions to anti-EGFR mAbs

Cetuximab[1]

- Medium to high-potency topical corticosteroids or oral tetracyclines have been used for the treatment of skin reactions
- According to clinical practice guidelines prophylactic use of oral tetracyclines (6–8 weeks) and topical application of 1% hydrocortisone cream with moisturiser should be considered

Panitumumab[2]

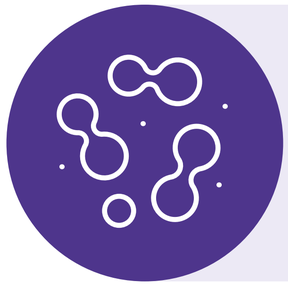
- Treatment should be based on severity and may include a moisturiser, sun screen (SPF >15), and topical steroid cream (maximum 1% hydrocortisone) and/or oral antibiotics (e.g. doxycycline)
- Patients experiencing a rash/skin reaction should be advised to apply moisturiser and sunscreen to the face, hands, feet, neck, back and chest every morning during treatment, and to apply the topical steroid to the face, hands, feet, neck, back and chest every night during treatment

EGFR, epidermal growth factor receptor; mAbs, monoclonal antibodies; SPF, sun protection factor.

1. Erbitux® SmPC. Merck; 2. Vectibix® SmPC. Amgen.

Acneiform rash – symptoms[1]

Rash is more or less confined to the face, the neck, the shoulders, the upper trunk and the scalp



Pustules may develop with subsequent crusting and a burning sensation

Can be associated with pain and itching

May arise a few days after treatment begins

1. Segaert S, van Cutsem E. *Ann Oncol.* 2005;16:1425-33.

Acneiform rash – grading[1]

NCI CTCAE version 5.0

Grade 1

Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness

Grade 2

Papules and/or pustules covering 10–30% BSA, which may or may not be associated with symptoms or pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering >30% BSA with or without mild symptoms

Grade 3

Papules and/or pustules covering >30% BSA, with moderate or severe symptoms; limiting self care ADL; associated with local superinfection with oral antibiotics indicated

Grade 4

Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms or pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences

ADL, activities of daily living; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous.

1. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (accessed August 2024).

Acneiform rash – general measures

Consider soap substitutes[1]

Consider tepid water to wash[1]

Avoid alcohol-based or perfumed products[2]

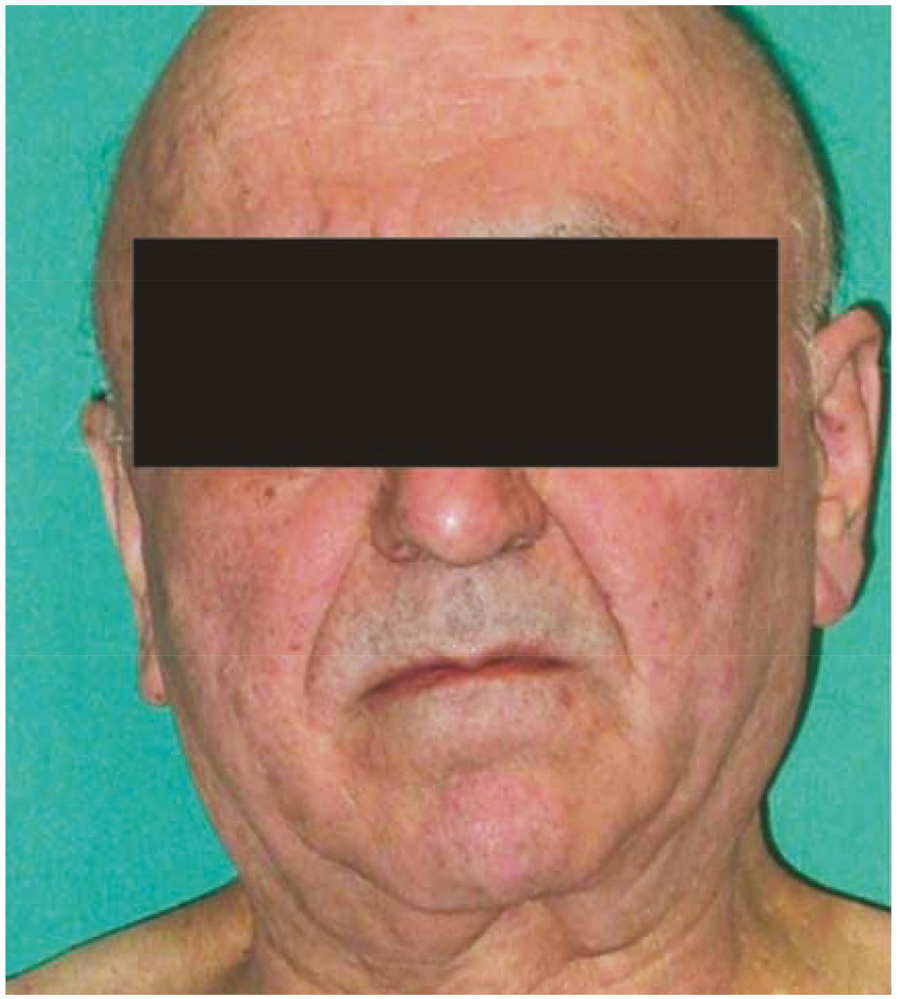
Patients may be advised to use a moisturising cream twice daily[2]

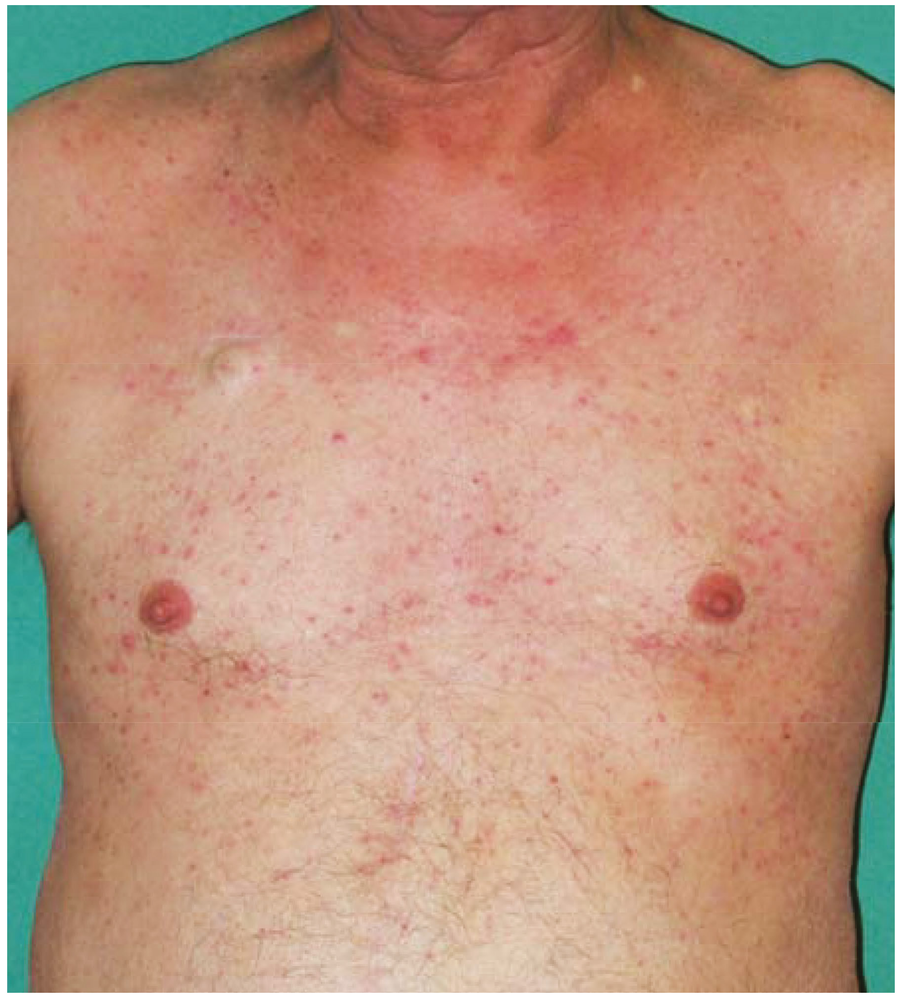
Sun exposure should be avoided and/or routine use of sun screen/sun block used[2]

Individual patient management should be determined by the treating healthcare professional and local protocol

1. Segaert S, van Cutsem E. *Ann Oncol.* 2005;16:1425-33; 2. NHS Scotland North Cancer Alliance Management of Chemotherapy Toxicity Guidelines 2018.

Acneiform rash – grade 1





Reproduced from Pinto C, *et al. The Oncologist.* 2011[1]

Grade of skin toxicity according to CTCAE (Common Terminology Criteria for Adverse Events).

1. Pinto C, *et al. The Oncologist.* 2011;16:228-38.

Acneiform rash – management of grade 1 rash[1]

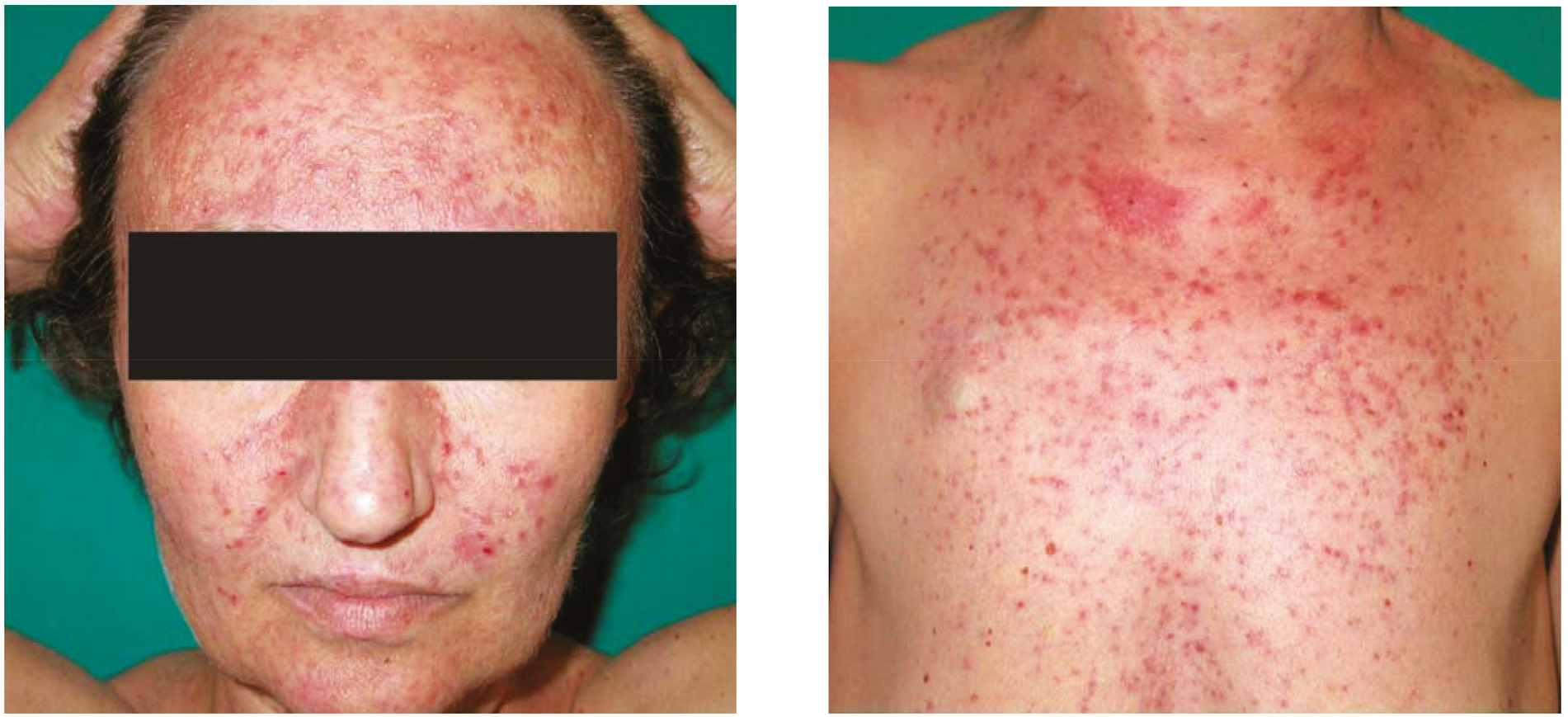
- No treatment may be necessary
- Ensure general care measures:
  - Good fluid intake
  - Avoid hot baths/tight clothes
  - Sun block, hat and avoid sun exposure
- Consider treatment with topical creams/lotions (alcohol free, hypoallergenic) and apply regularly to affected areas
- Consider oral anti-histamines if skin becomes itchy

Individual patient management should be determined by the treating healthcare professional and local protocol

Grade of skin toxicity according to CTCAE (Common Terminology Criteria for Adverse Events).

1. NHS Scotland North Cancer Alliance Management of Chemotherapy Toxicity Guidelines 2018.

Acneiform rash – grade 2



Reproduced from Pinto C, *et al. The Oncologist.* 2011[1]

Grade of skin toxicity according to CTCAE (Common Terminology Criteria for Adverse Events).

1. Pinto C, *et al. The Oncologist.* 2011;16:228-38.

Acneiform rash – management of grade 2 rash[1]

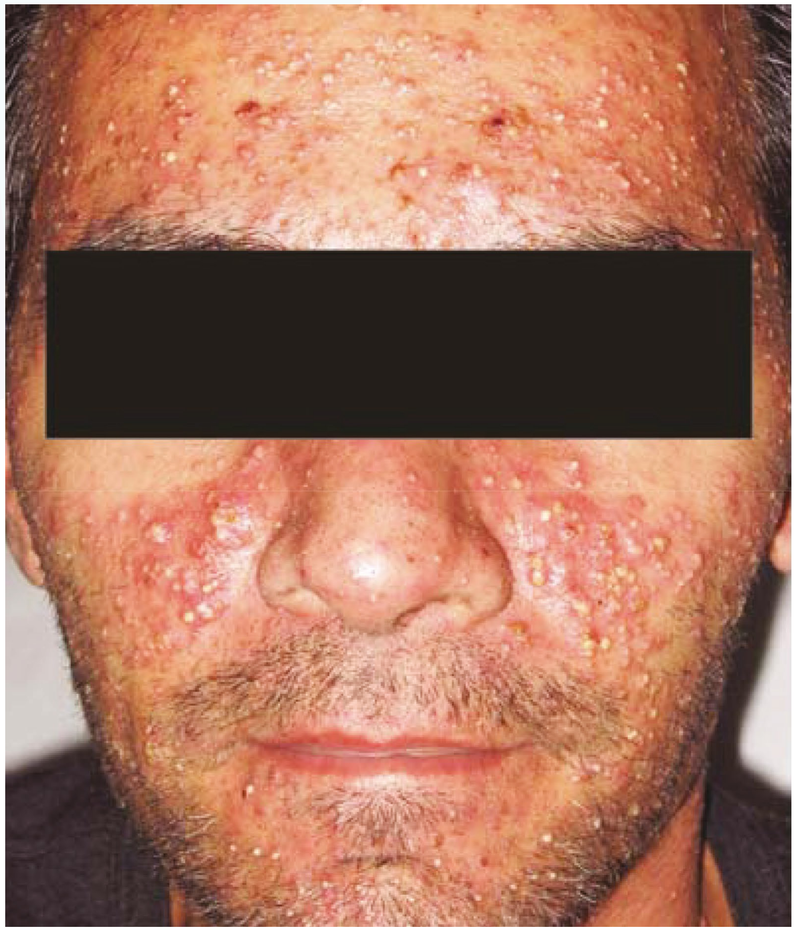
- Topical menthol cream
- An oral antihistamine (cetirizine, loratadine, hydroxyzine) when itch is present
- Systemic treatment – oral tetracyclines such as:
  - Doxycycline
  - Minocycline
  - Lymecycline
- When the acne-like rash is fading or becomes scaly, use moisturising creams

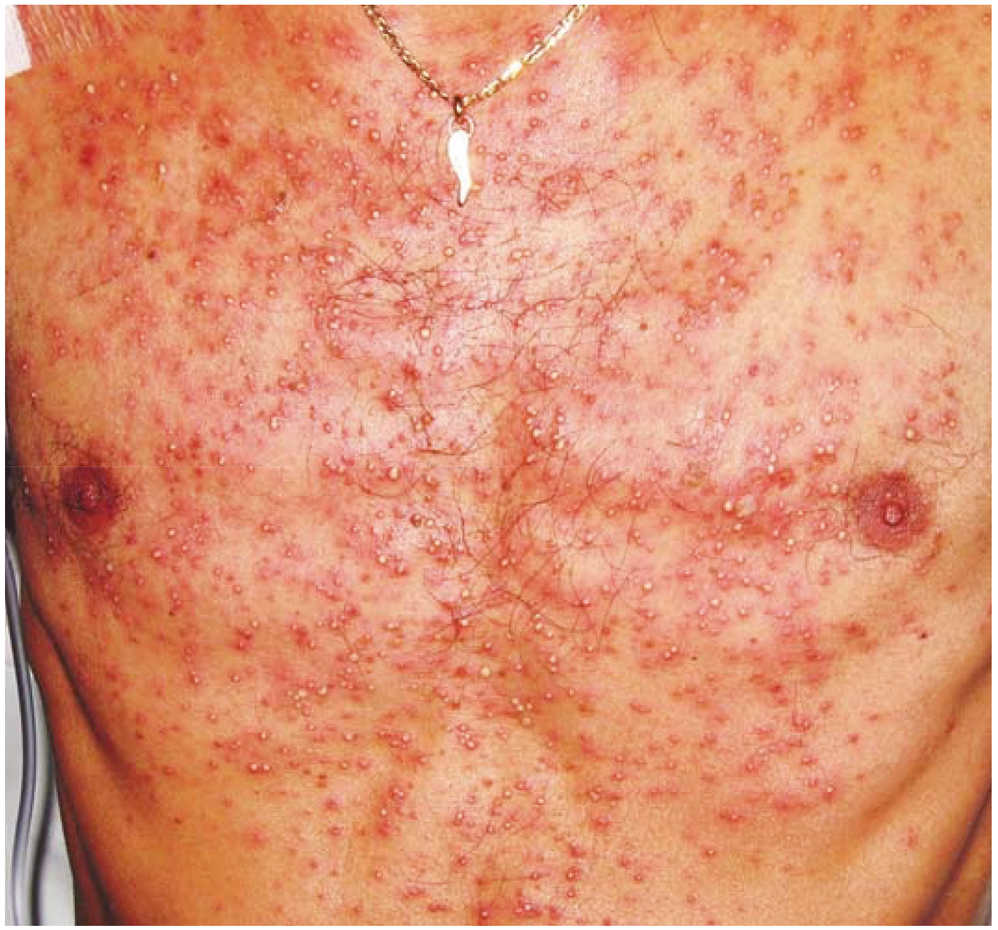
Individual patient management should be determined by the treating healthcare professional and local protocol

Grade of skin toxicity according to CTCAE (Common Terminology Criteria for Adverse Events).

1. Segaert S, van Cutsem E. *Ann Oncol.* 2005;16:1425-33.

Acneiform rash – grade 3





Reproduced from Pinto C, *et al. The Oncologist.* 2011[1]

Grade of skin toxicity according to CTCAE (Common Terminology Criteria for Adverse Events).

1. Pinto C, *et al. The Oncologist.* 2011;16:228-38.

Dry skin (xerosis) – symptoms[1]

Dry, scaly, itchy skin

Mainly on limbs or areas previously affected by acneiform eruption

Similar to atopic eczema

Painful fissures may develop on fingers and toes

Exacerbating factors which may accentuate the cutaneous dryness include: increasing age, previous therapy with cytotoxics and/or history of atopic eczema

1. Segaert S, van Cutsem E. *Ann Oncol.* 2005;16:1425-33.

Dry skin (xerosis) – grading[1]

NCI CTCAE version 5.0

Grade 1

Covering <10% BSA and no associated erythema or pruritus

Grade 2

Covering 10–30% BSA and associated with erythema or pruritus; limiting instrumental ADL

Grade 3

Covering >30% BSA and associated with pruritus; limiting self care ADL

ADL, activities of daily living; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events.

1. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (accessed August 2024).

Dry skin (xerosis) – general measures

Alcoholic gels or lotions should be avoided[1]

Patients may be advised to use a moisturising cream twice daily[2]

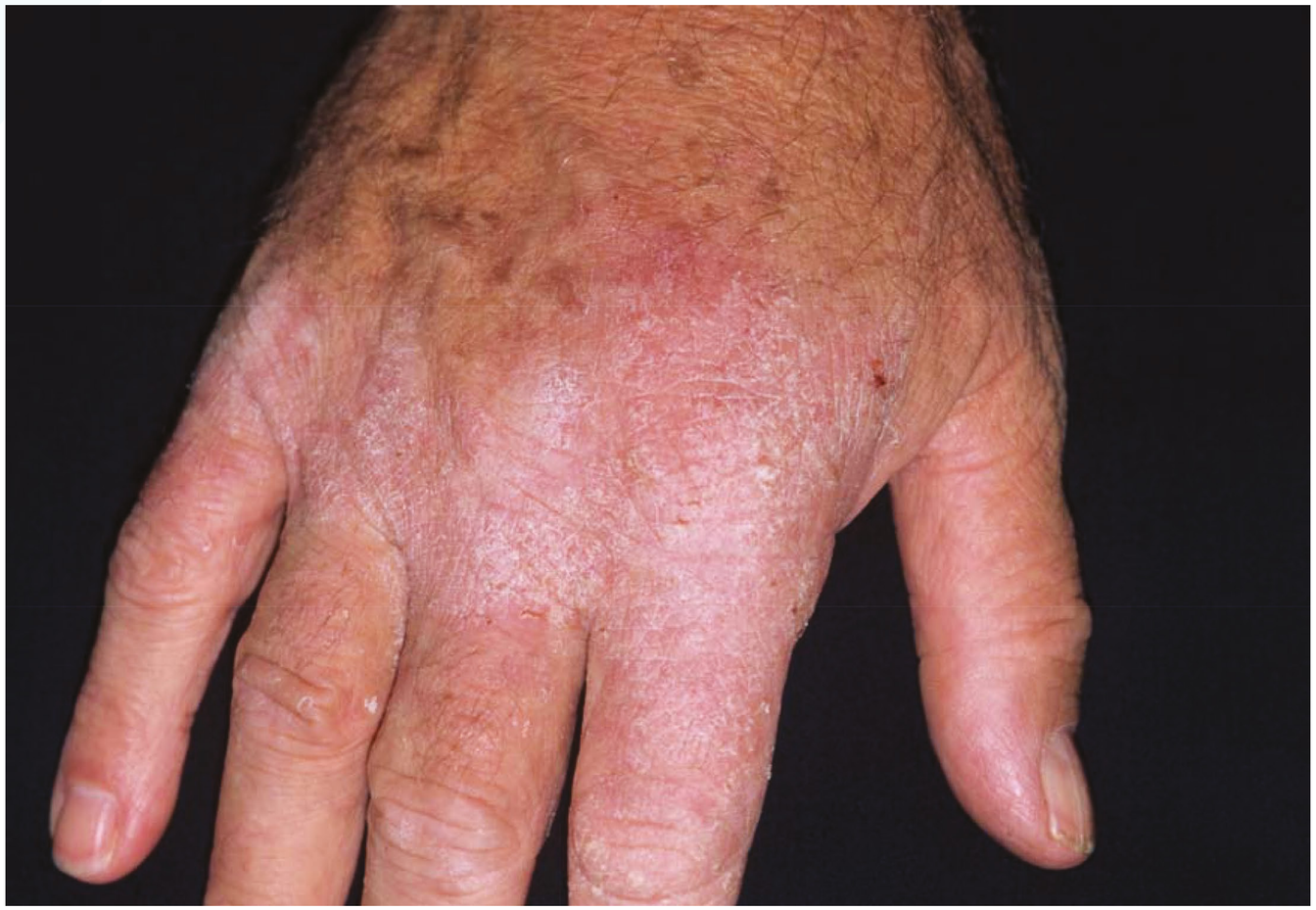
General hydration

Sun exposure should be avoided and/or routine use of sun screen/sun block used[2]

Individual patient management should be determined by the treating healthcare professional and local protocol

1. Segaert S, van Cutsem E. *Ann Oncol.* 2005;16:1425-33; 2. NHS Scotland North Cancer Alliance Management of Chemotherapy Toxicity Guidelines 2018.

Dry skin (xerosis)



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Dry skin (xerosis) – management

On development of grade ≥3 skin toxicity, follow dose interruption summary according to relevant Summary of Product Characteristics[1,2]

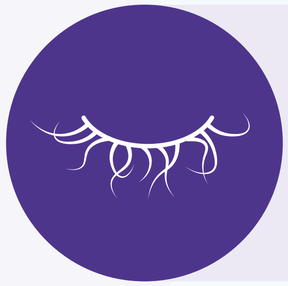
- Consider oil in water creams on face/chest/back[3]
- Greasy water in oil creams or even ointments may be used on limbs for moderate to severe xerosis[3]
- If eczema is present topical weak corticosteroids may be recommended for a short-term (1–2 weeks)[3]
- Fissures may be treated with:[3]
  - Propylene glycol 50% solution under plastic occlusion
  - Salicylic acid 10% ointment
  - Hydrocolloid dressing
  - Fludroxycortide (flurandrenolone) tape or liquid cyanoacrylate glue

Individual patient management should be determined by the treating healthcare professional and local protocol

Grade of skin toxicity according to CTCAE (Common Terminology Criteria for Adverse Events).

1. Erbitux® SmPC. Merck; 2. Vectibix® SmPC. Amgen; 3. Segaert S, van Cutsem E. *Ann Oncol.* 2005;16:1425-33.

Hair changes – symptoms[1]



Trichomegaly (long, curly, rigid eyelashes)

Eyebrows become thicker and more rigid

Scalp hairs grow more slowly and adopt a finer, more brittle and curly aspect

Mild hair loss can be seen on the scalp, arms or legs

Hypertrichosis (excessive hair growth)

1. Segaert S, van Cutsem E. *Ann Oncol.* 2005;16:1425-33.

Excessive hair growth (hypertrichosis) – grading[1]

NCI CTCAE version 5.0

Grade 1

Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal

Grade 2

Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact

CTCAE, Common Terminology Criteria for Adverse Events.

1. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (accessed August 2024).

Hair changes (trichomegaly)

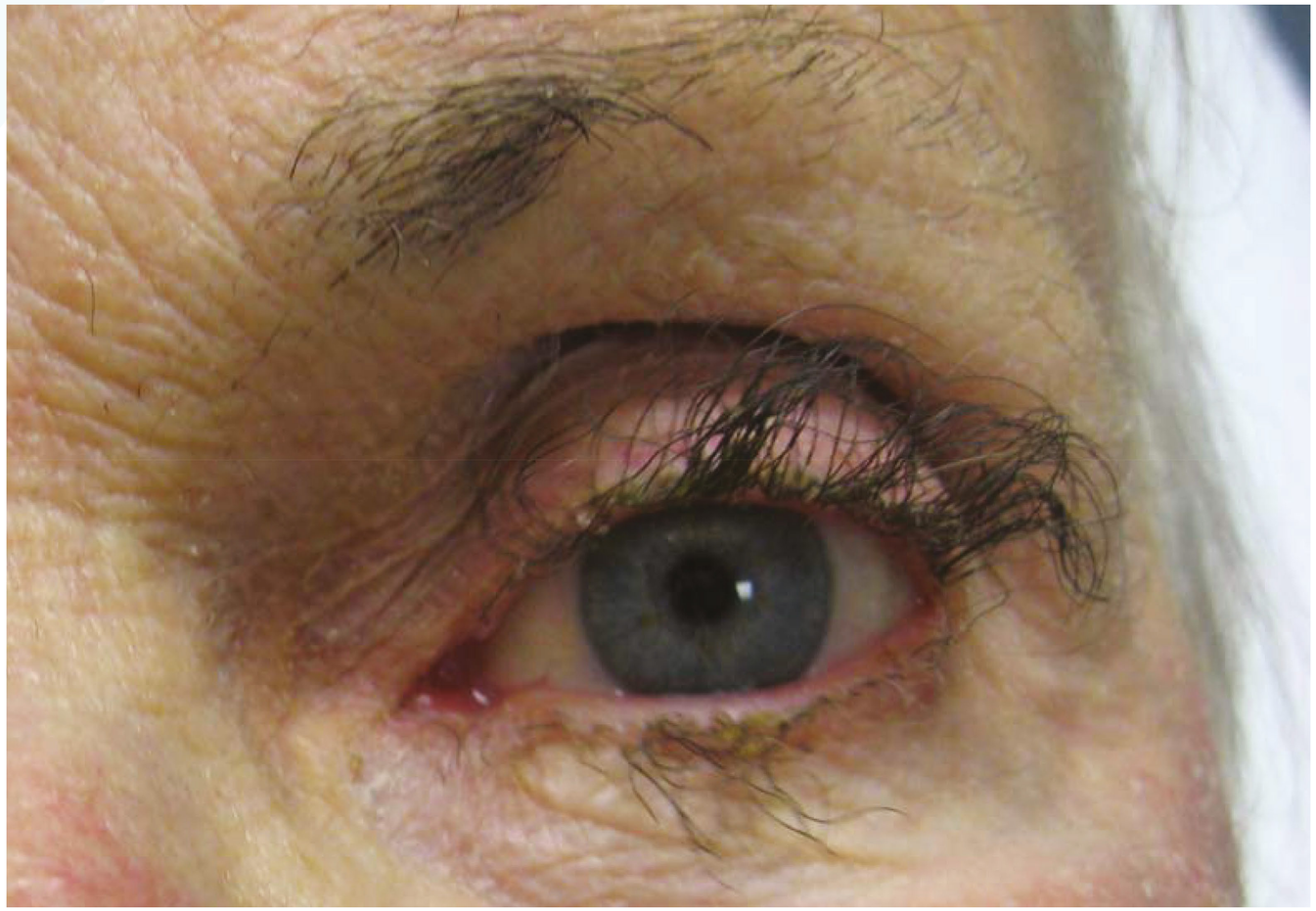


Image courtesy of Tripathi S, Oncotherapy Network. 2015.

Nail changes (paronychia) – symptoms

10-15%

Nail changes are seen in 10–15% of patients

Usually occurs after several weeks of treatment

The first sign is usually inflammation of the nail fold (mainly of the big toe; other toes and fingers may be involved as well)

Can be very painful and mimics an ingrown toenail in the severe cases where pyogenic granuloma of the nail fold develops

Secondary infection with *Staphylococcus aureus* is not uncommon and painful fissures sometimes arise in the nail folds

The nails tend to grow more slowly; they are more brittle and sometimes crack

1. Segaert S, van Cutsem E. *Ann Oncol.* 2005;16:1425-33.

Nail changes (paronychia) – grading[1]

NCI CTCAE version 5.0

Grade 1

Nail fold oedema or erythema; disruption of the cuticle

Grade 2

Localised intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold oedema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL

Grade 3

Operative intervention or IV antibiotics indicated; limiting self care ADL

ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous.

1. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (accessed August 2024).

Nail changes (paronychia) – general measures[1]

Advise patients to:

Avoid cutting nails too short or too straight

Avoid tightly fitting shoes and/or high heels

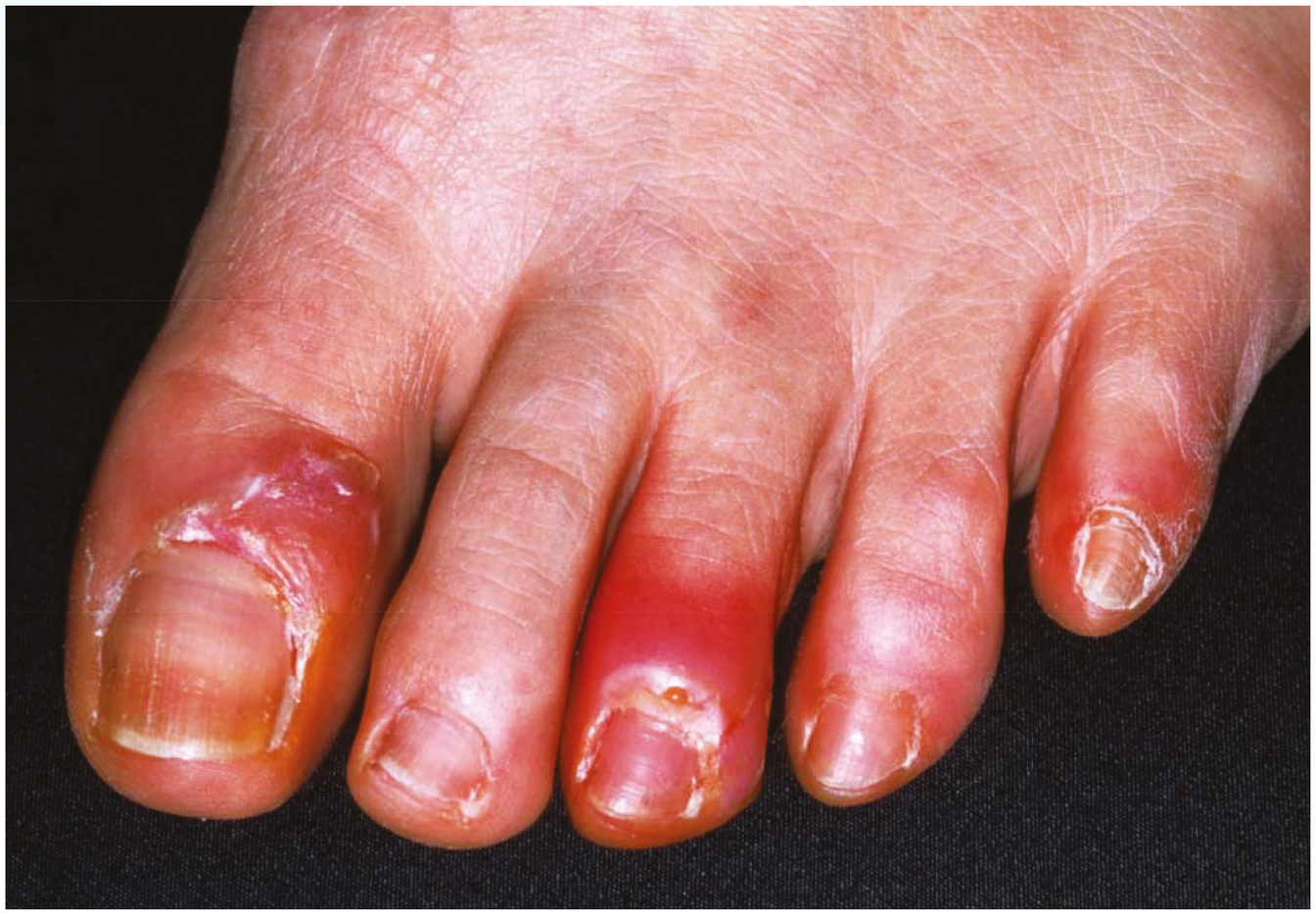
Wear gloves when washing dishes or using chemical agents

Use creams to keep skin moisturised

Individual patient management should be determined by the treating healthcare professional and local protocol

1. Reguiai Z, *et al. Support Care Cancer.* 2012;20:1395-1404.

Nail changes (paronychia)



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Nail changes (paronychia) – general measures

On development of grade ≥3 skin toxicity, follow dose interruption summary according to relevant Summary of Product Characteristics[1,2]

- Topical antiseptics or antibiotics (soaks and/or creams) may be used on a regular basis[3]
- A drying paste containing an antiseptic (chlorhexidine), an anti-fungal with activity against yeasts (nystatin) and in severe cases a topical corticosteroid may be used[3]
- In the case of secondary bacterial infection oral antibiotics may be administered[3]
- Silver nitrate application on a weekly basis may improve pyogenic granuloma[3]

Individual patient management should be determined by the treating healthcare professional and local protocol

Grade of skin toxicity according to CTCAE (Common Terminology Criteria for Adverse Events).

1. Erbitux® SmPC. Merck; 2. Vectibix® SmPC. Amgen; 3. Segaert S, van Cutsem E. *Ann Oncol.* 2005;16:1425-33.

Conclusions

EGFR inhibitors:

- Target pathways crucial for cancer cell growth and survival[1]
- EGFR inhibitor adverse events may result in decreased quality of life, and sometimes interruption of treatment[1]
- Strategies are available to prevent and manage skin-related adverse events[2]
  - If a patient experiences an intolerable or severe (grade ≥3; CTCAE) skin reaction to anti-EGFR mAb therapy, treatment must be interrupted[3,4]
  - Treatment may only be resumed if the reaction has resolved to grade 2 or lower, with dose modification for second, or subsequent, occurences[3,4]

CTCAE, Common Terminology Criteria for Adverse Events; EGFR, epidermal growth factor receptor.

1. Lacoutre ME, *et al. Nature Rev.* 2006;6:803-12; 2. Segaert S, van Cutsem E. *Ann Oncol.* 2005;16:1425-33; 3. Erbitux® SmPC. Merck; 4. Vectibix® SmPC. Amgen.

Prescribing Information- United Kingdom

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