Prevention and treatment of acneiform rash in patients treated with EGFR inhibitor therapies.

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Cancer Care Alberta

Alberta Provincial Thoracic Malignancies, Gastrointestinal, Head and Neck, and Breast Tumour Teams. Prevention and treatment of acneiform rash in patients treated with EGFR inhibitor therapies. Edmonton (Alberta): Cancer Care Alberta; 2020 Nov. 23 p. (Clinical practice guideline; no. SUPP-003) [67 references]

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Overview

Guideline Objective

To provide recommendations for the prevention and treatment of rashed caused by epidermal growth factor receptor (EGFR) inhibitor therapy

Patient Population

Adult cancer patients treated with EGFR inhibitors (i.e. afatinib, cetuximab, erlotinib, gefitinib, lapatinib, osimertinib, panitumumab, pertuzumab) either alone or in combination with other treatment

Recommendations

Recommendation Statements

1. Grading

1. Accurate grading of acneiform rash associated with epidermal growth factor receptor (EGFR) inhibitors is essential to ensure timely and appropriate interventions. We recommend using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), which is the most widely used classification system in clinical trials. (**Level of Evidence: V; Strength of Recommendation: C**)

   CTCAE defines acneiform rash as a disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, and upper chest and back. Refer to Table 2 in the original guideline for the NCI CTCAE grades for acneiform rash.

2. Rash and Response to Treatment Relationship

1. Rash occurrence has been statistically associated with efficacy of EGFR targeted therapies. However, we cannot conclude from these studies that EGFR inhibitor therapy is ineffective if no or only mild rash occurs. (**Level of Evidence: I; Strength of Recommendation: A**)

2. The goal of all cancer treatment is to minimize toxicity, maximize treatment adherence, and maintain a good health-related quality of life. Therefore, before starting treatment with an EGFR inhibitor clinicians should explore patient tolerance for cutaneous side effects through a discussion that includes occurrence, timing, severity, prevention and management of acneiform rash. (**Level of Evidence: V; Strength of Recommendation: B**)

3. EGFR inhibitors should be administered at their maximum tolerable doses to obtain the most effective outcomes and should be accompanied with appropriate supportive care or preventive measures to counteract the rash. (**Level of Evidence: II; Strength of Recommendation: B**)

3. Prevention of Rash

1. Before starting treatment with EGFR inhibitors, clinicians should perform an assessment of patients for pre-existing cutaneous conditions (e.g., psoriasis, acne

vulgaris, rosacea) that could worsen with exposure to EGFR inhibitors. (**Level of Evidence: V; Strength of Recommendation: B**)

2. Patients should be informed about general skin care practices to prevent or reduce the severity of acneiform rash, including: (**Level of Evidence: II; Strength of Recommendation: B**)

    - Use alcohol-free emollients for overall skin moisturization (i.e., creams, ointments)
    - Avoid popping acne pustules and using over-the-counter acne medications
    - Adequately hydrate
    - Apply broad spectrum (Ultraviolet A [UVA], Ultraviolet B [UVB]) sunscreens before going outdoors and avoid excessive sun exposure
    - Avoid hot water (i.e., use lukewarm water when showering, washing dishes)
    - Avoid tight-fitting clothing or irritating fabrics (e.g., wool)

3. For most patients starting EGFR-inhibitor therapy, antibiotic prophylaxis can be used concomitantly with a topical steroid (1% hydrocortisone cream) for the first six weeks to reduce the incidence and severity of acneiform rash and improve quality of life. In this role, the antibiotics are used for their anti-inflammatory properties and not their antimicrobial effects. We recommend second-generation tetracyclines, either minocycline or doxycycline 100-200 mg daily (single or divided doses). While minocycline is less photosensitizing, doxycycline has a more favorable safety profile (**Level of Evidence: I; Strength of Recommendation: A**). Although rare, for patients with allergies or intolerance to tetracyclines, erythromycin 500 mg twice a day or trimethoprim 160 mg/sulfamethoxazole 800 mg twice a day may be used as an alternative to minocycline or doxycycline. (**Level of Evidence: V; Strength of Recommendation: C**)

4. Studies have been unable to demonstrate a clinically significant benefit of adding tazarotene cream, dapsone gel, and vitamin K1 cream to minocycline or doxycycline. Similarly, topical erythromycin has not been shown to be an effective replacement for oral doxycycline, and therefore these drugs are not recommended. (**Level of Evidence: II; Strength of Recommendation: C [dapsone, vitamin K1] and D [tazarotene, erythromycin]**)

4. Management of Rash

The management of acneiform rash induced by EGFR inhibitors is largely based on small-scale prospective trials, case reports and case series. As a result, management approach varies (refer to Appendix C in the original guideline for relevant guidelines and consensus statements published within the last 10 years). The recommendations presented below are a consensus of members of the Alberta Provincial Tumour Teams who have experience prescribing EGFR inhibitors and/or treating skin conditions (refer to Appendix A in the original guideline).

1. **General recommendations**. Overall management strategy for acneiform rash should be individualized and will depend on the type, severity, location and need to continue treatment. Consultation with a dermatologist is recommended, particularly for rash that does not improve within one to two weeks of treatment or if the patient is severely symptomatic. (**Level of Evidence: II; Strength of Recommendation: B**)

2. **Grade 1 rash**. Patients should continue EGFR-inhibitor therapy at the prescribed dose. We recommend treatment with topical clindamycin 2% plus hydrocortisone 1% lotion twice daily for four weeks. If after four weeks of treatment the rash has not improved or has worsened, patients should be treated for a Grade 2 rash. (**Level of Evidence: V; Strength of Recommendation: C**)

3. **Grade 2 rash**. Patients should continue EGFR-inhibitor therapy at the prescribed dose. We recommend treatment with topical clindamycin 2%, hydrocortisone 1% lotion plus either oral minocycline 100 mg twice daily or doxycycline 100 mg twice daily for four weeks, if not used prophylactically. If after four weeks of treatment the rash has not improved or has worsened, patients should be treated for a Grade 3-4 rash. (**Level of Evidence: V; Strength of Recommendation: C**)

4. **Grade ≥3 rash**. A dose reduction of EGFR-inhibitor therapy, as per label, may be required (refer to Appendix D in the original guideline). Obtain bacterial/viral culture if infection is suspected. We recommend treatment with topical clindamycin 2%, hydrocortisone 1% lotion plus either oral minocycline 100 mg twice daily or doxycycline 100 mg twice daily for four weeks, plus oral prednisone up to 0.5 mg/kg daily for seven to 14 days. Referral to a dermatologist is recommended if rash does not improve after four to eight weeks. (**Level of Evidence: IV; Strength of Recommendation: C**)

    - If after four weeks of treatment the rash does not improve or worsens, low-dose isotretinoin (20 to 30 mg/d) or acitretin (25 mg/d) may be considered; evidence for its efficacy is however based on case series. (**Level of Evidence: V; Strength of Recommendation: C**)

- If the rash still does not improve or worsens despite dose modification and various treatment approaches (i.e., antibiotics, corticosteroids, isotretinoin, acitretin) discontinuation of EGFR inhibitor treatment may be necessary. (**Level of Evidence: V; Strength of Recommendation: B**)

5. **Secondary infection**. While pustules are generally sterile, secondary infection with bacteria, dermatophytes, or viruses may occur. Antibiotic selection for streptococcal or staphylococcal infections (culture proven with a swab), should be based on antimicrobial sensitivities. If pathogens other than streptococcal or staphylococcal are isolated, oncologists should ideally consult with a dermatologist for treatment advice (e.g., gram-negative microbes/other, saprophytic and dermatophyte fungi and yeasts). (**Level of Evidence: V; Strength of Recommendation: C**)

Evidence Rating Scheme

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Recommendation Rating Scheme

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally, not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Related Content

Supporting Documents

- Literature Review: EGFR Inhibitor Therapy and Acneiform Rash; 2020 Nov.

Implementation Tools

No implementation tools available.

Patient Education

No patient education materials available.

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TRUST Scorecard

Composition of Guideline Development Group (GDG)

Multidisciplinary GDG Members	**Yes**
Methodologist Involvement	**Yes**
Incorporation of Patient and Public Perspective	

Systematic Review of Evidence

Literature Search	
Study Selection	
Evidence Synthesis	

Foundations for Recommendations

Strength of Evidence Grade	
Description of Benefits and Harms of Recommendations	
Summary of Evidence Supporting Recommendations	
Strength of Recommendations Rating	
Clear Articulation of Recommendations	

Funding Source

Yes

Disclosure and Management of Financial Conflicts of Interests

External Review

Updating