



Management of EGFR TKI–induced dermatologic adverse events

B. Melosky MD, N.B. Leigh MD,†
J. Rothenstein MD,‡ R. Sangha MD,§
D. Stewart MD,|| and K. Papp MD#*

ABSTRACT

Targeting the epidermal growth factor receptor (EGFR) pathway has become standard practice for the treatment of advanced non-small-cell lung cancer. Compared with chemotherapy, EGFR tyrosine kinase inhibitors (TKIs) have been associated with improved efficacy in patients with an *EGFR* mutation. Together with the increase in efficacy comes an adverse event (AE) profile different from that of chemotherapy. That profile includes three of the most commonly occurring dermatologic AEs: acneiform rash, stomatitis, and paronychia. Currently, no randomized clinical trials have evaluated the treatments for the dermatologic AEs that patients experience when taking EGFR TKIs. Based on the expert opinion of the authors, some basic strategies have been developed to manage those key dermatologic AEs. Those strategies have the potential to improve patient quality of life and compliance and to prevent inappropriate dose reductions.

KEY WORDS

Non-small-cell lung cancer, adverse events, acneiform rash, paronychia, stomatitis, EGFR TKIs

1. INTRODUCTION

Treatment of non-small-cell lung cancer (NSCLC) with oral agents that target the epidermal growth factor receptor (EGFR) pathway has become a standard therapy for patients whose tumours have an *EGFR* gene mutation¹. The EGFR tyrosine kinase inhibitors (TKIs) block the adenosine triphosphate binding site of the intracellular kinase domain of EGFR and prevent phosphorylation, thereby inhibiting signal transduction and subsequent cell growth and proliferation^{2–4}.

Two types of EGFR TKIs have been developed: reversible and irreversible EGFR TKIs. Two reversible EGFR TKIs are currently approved by Health Canada for the treatment of patients with advanced NSCLC: gefitinib is approved in the first-line setting for patients whose

tumours are *EGFR*–mutation positive, and erlotinib is approved in the second- and third-line settings in unselected patients after chemotherapy failure¹. Gefitinib and erlotinib compete reversibly for the adenosine triphosphate binding site of the kinase domain of EGFR. After treatment with a reversible EGFR TKI, patients frequently become resistant to those agents because of a secondary mutation in the receptor's tyrosine kinase domain. In approximately half the cases of acquired resistance, the cause is a missense T790M mutation⁴.

To overcome resistance, the newer EGFR TKIs that have been developed bind irreversibly to the active site of the kinase domain. The newer agents include afatinib and dacomitinib. Afatinib is an ErbB family blocker that has been shown to be highly selective for EGFR, HER2 (the human epidermal growth factor receptor, ErbB2), and HER4 (ErbB4)^{5,6}. Afatinib is approved by Health Canada as monotherapy in EGFR TKI–naïve patients with metastatic lung adenocarcinoma who have an activating *EGFR* mutation. Like afatinib, dacomitinib is an irreversible pan-ErbB inhibitor that targets EGFR, HER2, and HER4⁷.

The primary dermatologic adverse event (AE) associated with reversible and irreversible EGFR TKIs is acneiform rash², which is characterized by an eruption of papules and pustules that typically appear on the face, scalp, upper chest, and back⁸. Additional AEs that are more commonly associated with irreversible EGFR TKIs are paronychia and stomatitis or mucositis⁹. Paronychia is a disorder characterized by an inflammatory process involving the soft tissues around the nails⁸. Stomatitis and mucositis are terms that are frequently used interchangeably. However, mucositis refers to an inflammation of the entire gastrointestinal tract; stomatitis refers specifically to inflammation of the oral mucosa^{8,10}.

Available evidence suggests that the severity of skin toxicity correlates positively with a response to therapy with EGFR TKIs^{11–13}. In the phase II IDEAL study, which evaluated the safety and efficacy of gefitinib in pretreated patients with NSCLC, skin toxicity was reported by 86% of patients who experienced symptom

improvement and by 58% of patients who experienced no symptom improvement¹⁴. A retrospective analysis of patients treated under the gefitinib Expanded Access Program showed that median survival was 10.8 months in patients who experienced a skin rash compared with just 4.0 months in patients not experiencing a skin rash ($p < 0.0001$)^{12,15}.

Similar results were seen in a retrospective study of erlotinib: after controlling for baseline factors, overall survival and progression-free survival showed a strong, positive correlation with the presence of rash—a correlation that increased with rash severity^{12,16}. The positive correlation between skin toxicity and clinical response suggests that rash could be a marker of EGFR TKI efficacy or adequate dosing.

2. PHYSIOLOGIC EFFECTS OF EGFR TKI INHIBITION

The EGFR is critical in the physiology and development of the epidermis, which is composed primarily of keratinocytes⁹. Undifferentiated proliferating keratinocytes, including those in the basal and suprabasal layers of the epidermis, express EGFR, which stimulates epidermal growth, promotes differentiation, and accelerates wound healing. Use of an EGFR TKI affects epidermal-derived tissues; effects include impaired keratinocyte growth, migration, and chemokine expression, which leads to inflammatory cell recruitment and cutaneous injury, including symptoms of rash and periungual inflammation. Those effects result from inhibition of pathways downstream of EGFR, such as the MAPK pathway^{1,17}.

2.1 Incidence of Dermatologic AEs

In phase III clinical trials, the incidence of acneiform rash varied from 37% to 76% in patients treated with reversible EGFR TKIs and from 69% to 89% in patients treated with the irreversible EGFR TKI afatinib (Table I). In phase II trials with dacomitinib, the incidence of acneiform rash was comparable to that in the phase III afatinib trials. In the case of gefitinib, the incidence of rash appeared to be related to dose. The incidence of stomatitis or mucositis in patients participating in phase III clinical trials of reversible EGFR TKIs varied from 6% to 19%. However, the incidence was higher in phase III clinical trials of afatinib, ranging from 51% to 72%. Similarly, the incidence of paronychia or nail effects was lower with gefitinib (3%–14% of patients) than with afatinib (33%–57% of patients). The higher incidence of dermatologic AEs seen with irreversible EGFR TKIs might be attributable to the covalent bond formed between the TKI and EGFR, which prolongs the effect of the TKI⁶.

In the LUX-Lung 3 trial of afatinib compared with pemetrexed–cisplatin chemotherapy, the all-grade incidences of acneiform rash, stomatitis or mucositis,

and paronychia (89.1%, 72.1%, and 56.8% respectively) were higher than the all-grade incidences of the same AEs reported in the LUX-Lung 6 trial (80.8%, 51.9%, and 32.6% respectively), which compared afatinib with gemcitabine–cisplatin chemotherapy^{50,51}. The differences in the two trials were the ethnic origins of the patient populations and the types of chemotherapy given, which would not affect the AE profile for patients in the afatinib arm. A recent analysis analyzed the incidence of the AEs in the two trials by ethnicity: the patient population in LUX-Lung 3 was approximately 72% East Asian, 26% white, and 2% other; the patient population in LUX-Lung 6 was entirely Asian^{50,51}. Overall rates of stomatitis or mucositis (65.3% vs. 39.1%) and paronychia (45.8% vs. 35.9%) were higher in Asian than in non-Asian patients. However, the rates of grade 3 events were low and comparable between those groups⁵⁶.

2.2 Acneiform Rash

2.2.1 Assessment and Grading

Acneiform rash usually develops in stages. In week 1, the patient experiences sensory disturbance, erythema, and edema; a papulopustular eruption follows in week 2. In week 4, crusting occurs, and in weeks 4–6, if the rash has been treated successfully, a background of erythema and dry skin occurs where papulopustular eruptions had previously been seen¹. Rash typically occurs on the face, shoulders, upper back, and upper chest. However, dry itchy skin can occur on the arms and legs of approximately 35% of patients and can become infected with the herpes simplex virus or *Staphylococcus aureus*¹¹. Acneiform rash seems to dissipate entirely once the EGFR TKI is discontinued^{11,12}.

For the first 6 weeks, patients should be closely followed each week and should contact their health care provider if rash becomes problematic. Patient education about EGFR TKI–induced rash should ideally begin before treatment initiation and continue throughout treatment. It is important to tell patients that EGFR TKI–induced rash is a common AE and that it might indicate efficacy of treatment. To prevent dose reduction or discontinuation of the EGFR TKI, it is important that patients know to report and obtain early treatment for rash². The impact of dose reduction on the clinical course of skin lesions has not been published and requires further investigation⁵⁷.

The most common grading system for acneiform rash is the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events*⁸ (Table II, Figure 1). The grade is determined in part by the percentage of body surface area covered in papules or pustules. Other considerations are psychosocial impact, extent of superinfection, and interference with daily activities. Grade 4 is considered life-threatening, and grade 5 is death.

TABLE I Incidence of three adverse events accompanying the administration of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in selected clinical trials in non-small-cell lung cancer^a

EGFR TKI and dose	Study type and dose	Incidence of adverse event by grade (%)					
		Acneiform rash		Stomatitis or mucositis ^b		Paronychia or nail effects ^b	
		All	≥3	All	≥3	All	≥3
Erlotinib 150 mg	All	33–79	3–10	9–19	<1–32	15	0
	Phase III	62–76	7–10	19	<1	NR	NR
Gefitinib 250 mg and 500 mg	All	34–75	0–13	6–17	<1	3–14	<1
	250 mg	34–66	0–4	6–17	<1	3–14	<1
	500 mg	57–75	4–13	NR	NR	NR	NR
	Phase III						
	250 mg	37–66	2–4	6–17	0–3	3–14	0–1
	500 mg	57–67	12–13	NR	NR	NR	NR
Afatinib 40 mg and 50 mg	All	69–94	7–28	50–90	0–10	33–85	0–11
	40 mg	69–90	7–16	50–72	0–9	33–80	0–11
	50 mg	78–94	14–28	61–90	3–10	39–86	5–8
	Phase III						
	40 mg	69–89	10–16	51–72	5–9	33–57	0–11
	50 mg	78	14	61	3	39	5
Dacomitinib 30 mg and 45 mg	All	68–100	0–15	15–46	0–3	NR	NR
	30 mg	69	0	15	0	NR	NR
	45 mg	68–100	15	46	3	NR	NR

^a Adapted and updated from Hirsh, 2011^{2,3,7,14,18–55}.

^b Grouped term.

NR = not reported.

TABLE II Common Terminology Criteria for Adverse Events grading system for acneiform rash⁸

Grade 1	<ul style="list-style-type: none"> Less than 10% of the body surface area is covered in papules or pustules (or both), which may or may not be associated with symptoms of tenderness or pruritus.
Grade 2	<ul style="list-style-type: none"> Between 10% and 30% the body surface area is covered in papules or pustules (or both), which may or may not be associated with symptoms of tenderness or pruritus. Associated with psychosocial impact. Limits instrumental activities of daily living.
Grade 3	<ul style="list-style-type: none"> More than 30% of the body surface area is covered in papules or pustules (or both) which may or may not be associated with symptoms of tenderness or pruritus. Associated with local superinfection, with oral antibiotics indicated. Limits self-care activities of daily living.
Grade 4	<ul style="list-style-type: none"> Any percentage of the body surface is covered in papules or pustules (or both), which may or may not be associated with symptoms of tenderness or pruritus. Associated with extensive superinfection, with intravenous antibiotics indicated. Life-threatening consequences.
Grade 5	<ul style="list-style-type: none"> Death

2.2.2 Management

Prophylactic Management Strategies: Two randomized double-blind studies whose goal was to determine if prophylactic tetracycline diminished the severity

of EGFR TKI-induced rash have been completed. The studies compared tetracycline (500 mg twice daily) given prophylactically (that is, before the EGFR TKI was started) with placebo^{58,59}. The results of the

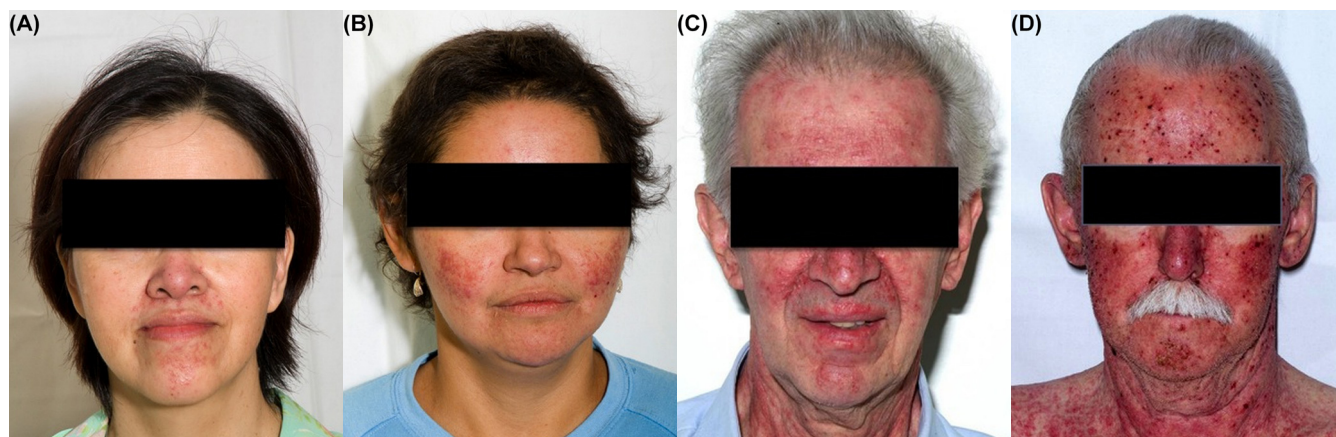


FIGURE 1 Acneiform rash induced by epidermal growth factor receptor tyrosine kinase inhibitors. (A) Grade 1, gefitinib. (B) Grade 2, erlotinib. (C) Grade 3, erlotinib. (D) Grade 4, erlotinib.

studies showed that tetracycline did not prevent rash, reduce rash severity, or improve quality of life. Another study, the Pan-Canadian Rash Trial (<http://clinicaltrials.gov/ct2/show/record/NCT00473083>), investigated whether prophylactic minocycline has an effect on the overall incidence of rash. Patients starting erlotinib were randomized to receive prophylactic minocycline for 4 weeks, rash treatment according to grade, or no treatment unless rash was severe. Preliminary analysis suggested that prophylactic minocycline treatment does not affect efficacy outcomes and is associated with a decrease in severe rashes, making prophylactic minocycline an option for the management of EGFR TKI-induced rash.

Preventive Management Strategies: A number of preventive measures can be taken to reduce the risk of EGFR TKI-induced acneiform rash. Patients should be instructed to apply an alcohol- and perfume-free emollient cream twice daily, preferably to the entire body. Creams and ointments are preferred over lotions, because lotions could contain alcohol. Sunscreen should be applied to sun-exposed areas twice daily to prevent sunburn or excess sun exposure, which can worsen symptoms of rash. Finally, hot showers and products that dry the skin should be avoided^{1,2}.

Pharmacologic Management Strategies: Treatment algorithms for EGFR TKI-induced acneiform rash vary widely between the expert centres using those agents. Hydrocortisone 1% cream is commonly found in treatment algorithms for rash. However, if it is insufficient, use of a higher-potency topical steroid—such as hydrocortisone valerate twice daily as needed for grades 1–3 rash—can be helpful (Table III). In addition, for grades 2 and 3 acneiform rash, oral minocycline (100 mg twice daily for 4 weeks) should be added to the treatment regimen¹.

The dose of EGFR TKI should be maintained through grade 2 acneiform rash. However, for prolonged

TABLE III Treatment algorithm for acneiform rash

Mild (grade 1)	<ul style="list-style-type: none"> Maintain dose level of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Apply hydrocortisone valerate topically twice daily as needed.
Moderate (grade 2)	<ul style="list-style-type: none"> Maintain dose level of EGFR TKI. Oral minocycline 100 mg twice daily for 4 weeks AND hydrocortisone valerate topically twice daily as needed. For prolonged grade 2 rash, EGFR TKI can be temporarily discontinued until improvement to grade 1 or less. Reintroduce EGFR TKI at a dose of the physician's discretion.
Severe (grade 3)	<ul style="list-style-type: none"> Temporary discontinuation of EGFR TKI for 2–4 weeks. Upon improvement to grade 2 or less, reintroduce EGFR TKI at a dose of the physician's discretion. If toxicities do not worsen, escalate the dose. If no improvement, discontinue. Oral minocycline 100 mg twice daily for 4 weeks AND hydrocortisone valerate topically twice daily as needed.

grade 2 rash, the EGFR TKI can be temporarily discontinued until symptoms improve to grade 1 or less; it can then be reintroduced at a dose of the physician's discretion. If rash progresses to grade 3, the EGFR TKI should be temporarily discontinued (2–4 weeks) and then reintroduced at a dose of the physician's discretion. If no improvement occurs, the EGFR TKI should be discontinued¹.

2.3 Stomatitis or Mucositis

2.3.1 Assessment and Grading

Before the start of treatment with an EGFR TKI, the patient's oral cavity should be assessed to obtain a baseline for any changes that might occur with therapy¹⁰. Oral mucositis can occur as broad areas of erythema or aphthous-like stomatitis⁹. Stomatitis usually starts with asymptomatic redness and erythema; it can progress to the formation of white patches associated with minimal pain, eventually transitioning to acutely painful large continuous lesions¹⁰. Based on the clinical experience of the authors, abnormal tingling sensations in the mouth are often reported within the first week of treatment with an EGFR TKI.

The *Common Terminology Criteria for Adverse Events* grading system sets out five grades of oral mucositis (Table IV, Figure 2)⁸. Grade 1 is characterized as asymptomatic or mildly symptomatic, and grade 2 as moderate pain that does not interfere with eating and drinking. By grade 3, patients can experience severe pain that interferes with intake of food and drink, followed by grade 4, which is considered life-threatening. Grade 5 is death.

2.3.2 Management

Oral Hygiene: After an initial assessment of oral health before the start of therapy with an EGFR TKI, the oral cavity should be evaluated by a health care professional periodically throughout treatment and at treatment completion⁹.

A simple oral care regimen for patients includes brushing the teeth and tongue with a soft-bristle brush, flossing, rinsing (preferably with normal saline), and moisturizing. If unable to use a toothbrush, patients can use a foam swab [for example, Toothette (Sage Products, Cary, IL, U.S.A.)] or piece of gauze, which are softer and less abrasive. Commercial mouthwashes often contain alcohol, which can irritate and dry the mucosal tissue; they should

be avoided¹⁰. For mild stomatitis, a patient should perform oral care every 2–3 hours; for patients with moderate-to-severe symptoms, oral care should be performed every 1–2 hours¹⁰.

Pharmacologic Management Strategies: No randomized controlled trials have evaluated treatment for EGFR TKI-induced stomatitis or mucositis, which can range from painful lesions to general mouth sensitivity⁹. The recommendations in the treatment algorithm (Table V) are based on the expert opinion of the authors.

For general mouth sensitivity, patients can gargle with Tantum [benzylamine rinse (Angelini, Ancona, Italy): 15 mL for 30 seconds and spit out] 3 times daily as needed. Treatment for grade 1 stomatitis or mucositis is triamcinolone in dental paste applied 2–3 times daily as necessary, a therapy that is also used to reduce pain and inflammation from aphthous ulcers⁶⁰. Treatment for grade 2 stomatitis includes the same regimen of triamcinolone in dental paste, with the addition of either oral erythromycin (250–350 mg daily) or minocycline

TABLE IV *Common Terminology Criteria for Adverse Events* grading system for oral mucositis⁸

Grade 1	• Asymptomatic or mild symptoms; intervention not indicated.
Grade 2	• Moderate pain; not interfering with oral intake; modified diet indicated.
Grade 3	• Severe pain; interfering with oral intake.
Grade 4	• Life-threatening consequences; urgent intervention indicated.
Grade 5	• Death

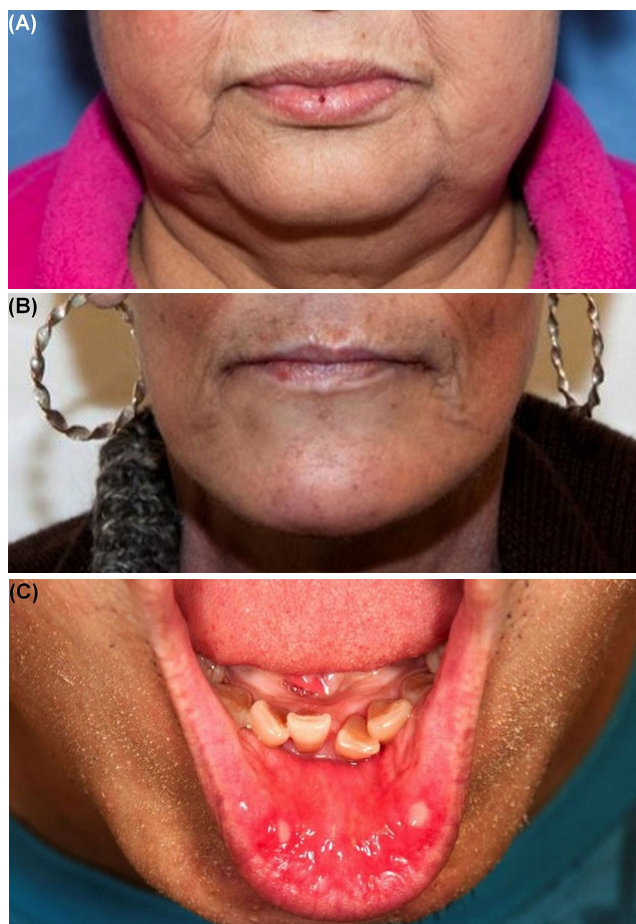


FIGURE 2 Stomatitis or mucositis induced by epidermal growth factor receptor tyrosine kinase inhibitors. (A) Grade 1, afatinib. (B) Grade 2, afatinib. (C) Grade 3, afatinib.

TABLE V Treatment algorithm for stomatitis or mucositis

Mild (grade 1)	<ul style="list-style-type: none"> Maintain dose level of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Apply triamcinolone in dental paste 2–3 times daily as needed.
Moderate (grade 2)	<ul style="list-style-type: none"> Maintain dose level of EGFR TKI. Apply triamcinolone in dental paste 2–3 times daily as needed AND oral erythromycin 250–350 mg daily OR minocycline 50 mg daily.
Severe (grade 3)	<ul style="list-style-type: none"> Temporary discontinuation of EGFR TKI for 2–4 weeks. Upon improvement to grade 2 or less, reintroduce EGFR TKI at a dose of the physician's discretion. If toxicities do not worsen, escalate the dose. If no improvement, discontinue. Apply clobetasol ointment, 2–3 times daily as needed AND oral erythromycin 500 mg daily OR minocycline 100 mg daily.

(50 mg daily). For grade 3, clobetasol ointment is used instead of triamcinolone in dental paste, and the erythromycin dose is increased to 500 mg daily or the minocycline dose to 100 mg.

As with acneiform rash, the dose of EGFR TKI is maintained for grades 1 and 2 stomatitis; the EGFR TKI is temporarily discontinued (2–4 weeks) for grade 3 events. Upon improvement to grade 2 or less, the EGFR TKI can be reintroduced at a dose of the physician's discretion. However, if no improvement is seen, the EGFR TKI should be discontinued.

2.4 Paronychia

2.4.1 Assessment and Grading

Acneiform rash typically appears early in treatment, but paronychial inflammation occurs after a longer period (that is, after several weeks or months of EGFR TKI therapy)^{1,61}. Nail changes are usually mild, but can also be symptomatic and severe^{1,62}. Paronychia affects the nails of the fingers and toes, most commonly occurring on the first digits⁹.

The *Common Terminology Criteria for Adverse Events* grading system for paronychia ranges from grade 1 to grade 3, instead of grades 1–5 (Table VI, Figure 3)⁸. Grade 1 paronychia is associated with nailfold edema or erythema and cuticle disruption. By grade 2, the nailfold edema or erythema is associated with pain. In grade 2 paronychia, discharge or nail-plate separation can also occur, and instrumental

TABLE VI *Common Terminology Criteria for Adverse Events* grading system for paronychia⁸

Grade 1	<ul style="list-style-type: none"> Nail fold edema or erythema; disruption of the cuticle.
Grade 2	<ul style="list-style-type: none"> Nail fold edema or erythema with pain; associated with discharge or nail plate separation. Limits instrumental activities of daily living. Localized intervention indicated; oral intervention indicated (for example, antibiotic, antifungal, antiviral).
Grade 3	<ul style="list-style-type: none"> Limits self-care activities of daily living. Surgical intervention or intravenous antibiotics indicated.
Grade 4	—
Grade 5	—

activities of daily living are limited. Local or oral intervention is indicated. Grade 3 paronychia is characterized by limitations in self-care activities of daily living, and surgical intervention could be indicated.

2.4.2 Management

As for stomatitis, no randomized controlled trials have evaluated treatments for paronychia. The recommendations in the treatment algorithm (Table VII) are based on the expert opinion of the authors.

Local Care Strategies: Local care strategies to manage paronychia include emolliation with petroleum jelly, cushioning of affected areas, nail trimming (no aggressive manicures), and the use of gloves when cleaning to avoid irritants. Antimicrobial soaks (for example, diluted white vinegar or diluted bleach in water) are recommended to help prevent superinfection⁹.

Pharmacologic Management Strategies: In the general population, acute paronychia is typically associated with *S. aureus* infection, and chronic paronychia is usually associated with *Candida albicans* (or *Monilia*) infection⁶³, indicating a potential need for antibiotic or antifungal interventions⁸. However, EGFR TKI-associated paronychia is sterile and corresponds with an unguinal-fold inflammation consisting primarily of plasma cells, lymphocytes, and neutrophils^{64,65}. To treat this type of paronychial inflammation, beta-methasone valerate for grades 1 and 2 and clobetasol cream for grade 3 should be applied 2 or 3 times daily as needed. If paronychia reaches grade 3, the EGFR TKI should be temporarily discontinued (2–4 weeks) until symptoms improve to grade 1 or less, when the drug can be reintroduced at a dose of the physician's discretion. If no improvement is seen during the temporary discontinuation period, the EGFR TKI

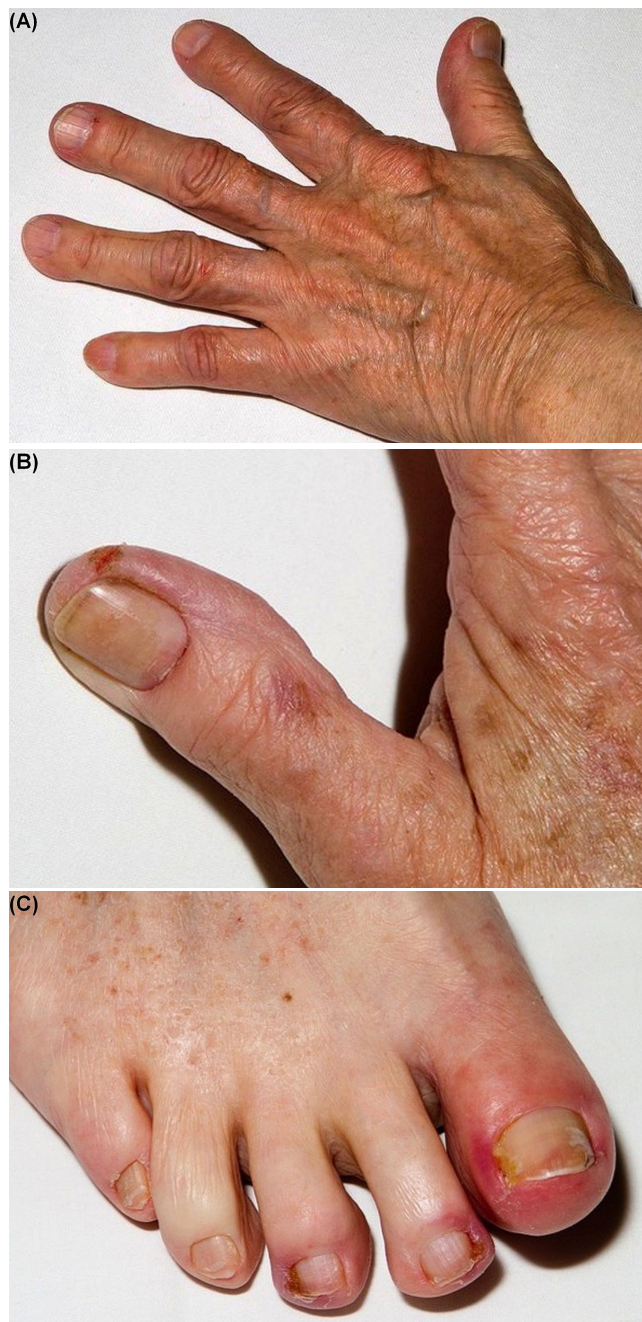


FIGURE 3 Paronychia or nail effects induced by epidermal growth factor receptor tyrosine kinase inhibitors. (A) Grade 1, erlotinib. (B) Grade 2, afatinib. (C) Grade 3, erlotinib.

should be stopped altogether. In cases of refractory paronychia, or if signs of a superinfection are present, topical antibiotics such as mupirocin ointment can be used.

3. SUMMARY

Three of the most common dermatologic AES associated with EGFR TKI therapy are acneiform rash,

TABLE VII Treatment algorithm for paronychia

Local care	<ul style="list-style-type: none"> • Petroleum jelly emolliation. • Antimicrobial soaks. • Cushioning of affected areas.
Mild-to-moderate (grade 1 or 2)	<ul style="list-style-type: none"> • Maintain dose level of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). • Apply betamethasone valerate 2–3 times daily as needed.
Severe (grade 3)	<ul style="list-style-type: none"> • Temporary discontinuation of EGFR TKI for 2–4 weeks. Upon improvement to grade 1 or less, reintroduce EGFR TKI at a dose of the physician's discretion. If toxicities do not worsen, escalate the dose. If no improvement, discontinue. • Apply clobetasol cream 2–3 times daily as needed.

stomatitis, and paronychia. These dermatologic AES can be significant and debilitating and can have a negative effect on the patient's quality of life^{57,65}. The potential for reduced treatment compliance resulting from EGFR TKI-induced AES can complicate disease management, especially given that the severity of some of the AES appears to correlate with treatment response⁶⁵. Current AE management strategies have been developed based on physician experience. However, as treatment with targeted agents becomes more common for patients with NSCLC, the most effective interventions for dermatologic AES will need to be determined through rigorous, systematic evaluation, so as to ensure patient compliance and improve quality of life.

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5. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: BM has received honoraria for advisory board participation from Eli Lilly, Hoffmann–La Roche, Pfizer, and Boehringer Ingelheim. JR has received honoraria from Eli Lilly, Boehringer Ingelheim, and AstraZeneca. KP has consulted for and received payment from 3M, Abbott, Akesis, Akros, Alza, Amgen, Astellas, Baxter, Boehringer Ingelheim, Celgene, Centocor, Cipher, Eli Lilly, Forward Pharma, Isotechnika, Janssen, Janssen Biotech (Centocor), Johnson and Johnson, Kataka, Kirin, Kyowa, Lypanosys, Meiji Seika

Pharma, Medical Minds, Merck, Mitsubishi Pharma, Novartis, Pfizer, Takeda, UCB, Vertex, and Wyeth. DS has consulted for, or been on the advisory boards of, Easton Associates, SAIC, Trinity Partners, Coleman Research Group, Frankel Group, Align2Action, Amgen Canada, Hoffmann–La Roche Canada, Pfizer Canada, Boehringer Ingelheim Canada, Transport Canada, and Guidepoint Global/Warburg Pincus; has had grants paid to his institution from the U.S. National Institutes of Health, the U.S. Department of Defense, AstraZeneca, Hoffmann–La Roche Canada, and Pfizer Canada; has been a speaker for Pfizer Canada, AstraZeneca Taiwan, University of Michigan/SWOG, Ventana, IASLC, University of Texas San Antonio, American Radium Society, and the 5th International Pulmonary Congress; and has received royalties from Springer. NBL and RS have no conflicts of interest to declare.

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Correspondence to: Barbara Melosky, BC Cancer Agency, 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6.

E-mail: bmelosky@bccancer.bc.ca

- * BC Cancer Agency, Vancouver, BC.
- † Princess Margaret Cancer Centre, University Health Network, Toronto, ON.
- ‡ R.S. McLaughlin Durham Regional Cancer Centre, Lakeridge Health, Oshawa, and Department of Oncology, Queen's University, Kingston, ON.
- § Cross Cancer Institute, Edmonton, AB.
- || The Ottawa Hospital and University of Ottawa, Ottawa, ON.
- # Probitry Medical Research, Waterloo, ON.