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REVIEW ARTICLE

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Management of epidermal growth factor receptor tyrosine kinase inhibitor-related cutaneous and gastrointestinal toxicities

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Abstract

Patients with advanced stage non–small cell lung cancer with sensitizing epidermal growth factor receptor (EGFR) mutations using EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib and afatinib as first-line treatment had better progression-free survival, overall response rate and quality of life than those on chemotherapy. Although EGFR TKIs are commonly associated with skin-related (rash, xerosis and paronychia) and gastrointestinal-related (diarrhea and stomatitis) adverse events (AEs), these effects are usually mild. But severe cases can occur, significantly affecting patient's well-being, treatment compliance and quality of life. Therefore, patient education, early diagnosis, and prophylactic treatment are important strategies to optimally manage EGFR TKI-related adverse effects. In this review, we summarize the commonly encountered EGFR TKI-related AEs and provide a current overview of AE management in local practice with a focus on Asian patients.

KEYWORDS

adverse drug events, gastrointestinal tract, mutations, non–small cell lung cancer, skin

1 | BACKGROUND

Eighty percent of lung cancers are advanced-stage non–small cell lung cancer (NSCLC).(1) Epidermal growth factor receptor (EGFR) gene mutation, which is a major and potent oncogenic driver in NSCLC is a therapeutic target, with EGFR tyrosine kinase inhibitors (EGFR TKIs), altering the pattern of care in patients with advanced stage NSCLC. With EGFR TKIs (erlotinib, gefitinib and afatinib) as first-line treatment for patients with advanced stage NSCLC with sensitizing EGFR mutations, higher progression-free survival, overall response rate and quality of life than chemotherapy can be achieved.[1] These drugs are generally well tolerated as they have a predictable toxicity profile and less serious toxicities than traditional cytotoxic chemotherapy.[2] Nevertheless, EGFR TKIs can still produce severe adverse events (AEs) and impair quality of life.

As EGFR is mainly expressed in epithelial cells, such as the skin and gastrointestinal tract, the most common AEs for EGFR TKIs are cutaneous and gastrointestinal related.[3] Cutaneous AEs are particularly troublesome as these affect a patient's psychosocial well-being and increase the risk of secondary skin infections, which ultimately affects dose intensity. A survey of 110 oncologists who administered EGFR inhibitor therapy revealed that rash caused 76% of patients to interrupt their therapy and approximately a third (32%) of patients to discontinue it altogether.[4] Cutaneous AEs caused 60% of participants to reduce therapy dose by 10–50%. EGFR TKI-related diarrhea also greatly affects quality of life, causing lethargy, sleep interruptions and major inconvenience to daily life as patients are reluctant to leave the house. Therefore, the prevention and management of AEs would improve the quality of life and treatment adherence of these patients.

TABLE 1 Time of onset and incidence of skin and gastrointestinal AE with treatments for non–small cell lung cancer

		Gefitinib		Erlotinib		Afatinib		Osimertinib	
	Adverse event	Time to onset, median (days)[12]	% of patients ($n = 607$)[13]	Time to onset, median (days)[12]	% of patients ($n = 83$)[14]	Time to onset, median (days)[12]	% of patients ($n = 229$)[15]	Time to onset, median (days)	% of patients ($n = 279$)[7]
Skin	Rash/acne	37	66.2	22	73	42	89.1	Data not available	34
	Dry skin	43	23.9	36	–	49	29.3		23
	Pruritus	31	19.4	22	–	55	18.8		13
	Paronychia	101	13.5	78	4	56	56.8		22
Gastrointestinal	Diarrhea	–	46.6	12(40)	21	3(6)	95.2		41
	Stomatitis/ mucositis	–	17	–	13	–	72.1		15

In this review, we provide an overview of the commonly occurring cutaneous and gastrointestinal AEs related to EGFR TKI treatment. In addition, we summarize the preventative and therapeutic measures for these AEs that are commonly practiced in Singapore. As it is also widely accepted that there are differences in skin biology between Asians and Caucasians, we would focus our discussion on Asian patients as earlier similar publications covered the Caucasian population.[5,6] We would place emphasis on patients who were treated with EGFR TKI as first line as they are more susceptible to AEs compared to patients in later line settings. Management of EGFR TKI-related AE is generally the same across the three TKIs although practices on the type of antibiotics and steroids used and when these are prescribed can vary.

The third-generation TKIs include as osimertinib (AZD9291), rociletinib (CO-1686), HM61713 (olmutinib), EGF816 and ASP8273 are mutant selective, targeting sensitizing EGFR mutations as well as T790M EGFR and is WT EGFR sparing, resulting in less off-target toxicities. Of the agents in this class, only osimertinib has been approved for advanced NSCLC with EGFR T790M mutation following acquired resistance to first- or second-generation EGFR TKIs. As such, we will include discussions on the management of AEs related to this agent. Given the mechanism of action, the AEs related to EGFR blockade with osimertinib such as skin rash, xerosis and paronychia are predictably lower than the previous generation of EGFR TKIs (Table 1). The frequency of diarrhea is 24–41% but grade 3 or more is rare (1–2%).[7–9] The principles of management of AEs related to the first- and second-generation EGFR TKIs can be applied to osimertinib.

2 | COMMONLY OCCURRING EGFR TKI-RELATED CUTANEOUS AES

As EGFR is involved in epithelial maintenance (i.e. epidermal growth, differentiation, wound healing and keratinocyte migration), it is critical in the physiology and development of the epidermis (which is composed primarily of keratinocytes).[5,10] An EGFR TKI impairs keratinocyte growth, migration and chemokine expression, resulting in inflammatory cell recruitment and cutaneous injury by inhibiting pathways downstream of EGFR, such as the mitogen-activated protein kinase (MAPK) pathway (Figure 1). Although not fully understood mechanistically, Asians have been consistently demonstrated to have more sensitive skin compared to Caucasians in studies investigating skin responses to irritants.[11] For this reason, we would expect differences in the manifestation of EGFR-TKI induced skin toxicity. In this section, we would describe commonly occurring EGFR TKI-related cutaneous AEs such as rash, xerosis, paronychia and scalp lesions exhibited in Asian patients. Table 1 is a summary of the onset timing and frequency of commonly occurring cutaneous AEs caused by first and second generation EGFR TKI.[12–15] As data on the time to onset for osimertinib is not available, we only report on the frequency of cutaneous AE that was recently revealed in the AURA3 trial.[7]

2.1 | Papulopustular (acneiform) rash

The earliest and most common EGFR TKI-related cutaneous AE is acneiform rash. The eruption generally evolves through four distinct phases[10,16]: (1) dysesthesia, erythema and edema as early as 1–2 weeks of first- and second-generation EGFR TKI treatment; (2) erythematous papules and pustules; (3) purulent crusts at 3–6 weeks and (4) telangiectasias. Patients will experience waxing and waning of lesions during the clinical course. Lesions can be painful and pruritic. Symptoms typically resolved within 4 weeks after EGFR TKI is ceased; but there could be partial or even complete resolution despite continued EGFR TKI therapy. Because EGFRs are highly expressed in sebaceous epithelium, eruptions are generally most concentrated in seborrheic areas such as the scalp, face, neck, chest and upper back. The periorbital region, palms and soles are usually spared.[17] The different degrees of severity of the papulopustular rash are illustrated in Figure 2.

2.2 | Xerosis

Abnormal keratinocyte differentiation due to EGFR TKIs can impair the epidermal barrier, decreasing loricrin, the main protein forming the scaffold for the epidermis.[18,19] This leads to xerosis caused by an unwoven epidermal layer that loses moisture. In this report, we refer to CTCAE v4.03 for the grading of xerosis, which describes dry skin covering <10% with no associated erythema or pruritus, 10–30% with erythema/pruritus and limiting instrumental activities of daily living (ADL) and >30% with pruritus and limiting self-care ADL for

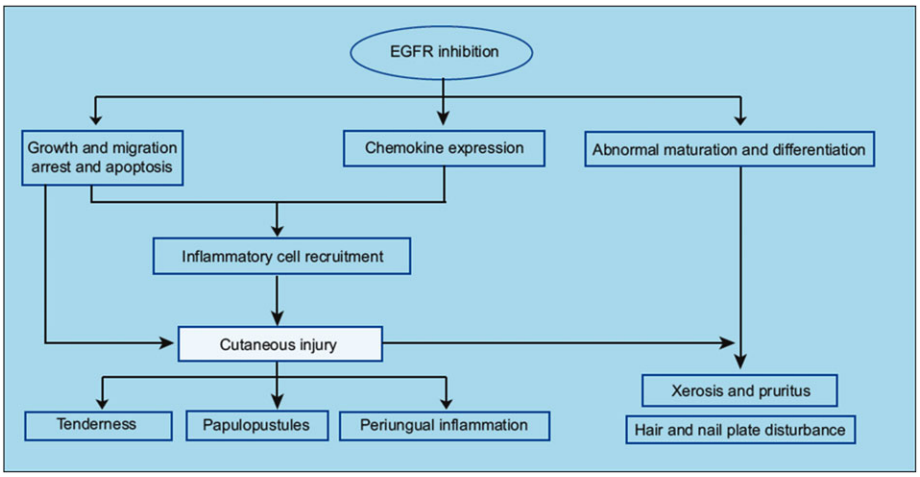

FIGURE 1 Pathogenetic mechanism of EGFR inhibition in cutaneous adverse reactions EGFR: epidermal growth factor receptor [Colour figure can be viewed at wileyonlinelibrary.com]

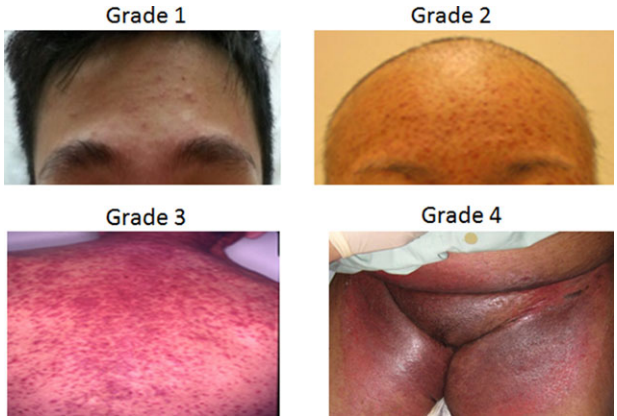

FIGURE 2 Severity grading of tyrosine kinase inhibitor-induced papulopustular rash; Grade 1: BSA < 10%; Grade 2: BSA 10–30%; Grade 3: BSA > 30%, erosions, vesicles and desquamation may be present; Grade 4: BSA > 30%, blistering, erosions, ulceration, epidermal denudation may be present. BSA, body surface area. [Colour figure can be viewed at wileyonlinelibrary.com]

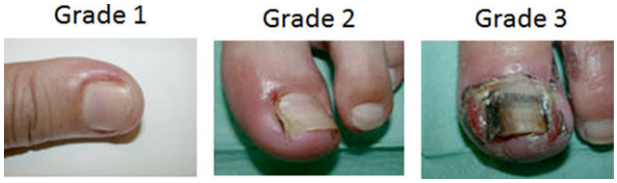

FIGURE 3 Severity grading of tyrosine kinase inhibitor-induced paronychia Grade 1: Nailfold edema and/or erythema with cuticle disruption; Grade 2: Painful nailfold bogginess and/or discharge with onycholysis; Grade 3: Ingrown nails with intense pain; pyogenic granuloma and/or exuberant periungual granulation tissue may be present. [Colour figure can be viewed at wileyonlinelibrary.com]

grade 1, 2 and 3, respectively. Xerosis is also considered to be associated with EGFR inhibitors, affecting almost all patients to variable degrees.[19] Xerosis generally occurs late, after the patient has been on anti-EGFR treatment for at least 30–60 days.[20] This condition usually follows or accompanies by acneiform eruption[20] and typically presents as dry, scaly, itchy skin on any part of the body. Some patients have reported vaginal and perineal dryness. Patients with xerosis may develop chronic asteatotic eczema which predisposes to secondary infections with *Staphylococcus aureus* or the *Herpes Simplex* virus.[21] There have also been incidences of severe cases of pulpitis sicca with painful rhagades.

2.3 | Paronychia

Between 10 and 15% of first and second generations EGFR TKI patients have paronychia; and this condition typically occurs later during treatment (i.e. 4–8 weeks).[22] Paronychia is graded by severity according to CTCAE v4.03 guidelines as illustrated in Figure 3. The big toe is commonly the first area to be affected, and when pyogenic granuloma develops on the nail fold, patient can experience severe pain.[23] Nail matrix inflammation may result in onycholysis or onychodystrophy.

2.4 | Scalp lesions

The EGFR TKIs have been linked to severe scalp inflammation and hair loss (scarring or non-scarring alopecia).[24–27] Folliculitis decalvans is a severe form of scarring involving the scalp.[20] Generally, 5–6% of the patients develop alopecia 2–4 months after therapy is started, whereas hirsutism (hair curling and rigidity, facial hypertrichosis and trichomegaly) can appear 1–2 months after therapy is started. If trichomegaly involves the eyelashes, eye irritation and conjunctivitis can occur.[28–30] Alopecia associated with EGFR TKI primarily consists of catagen/telogen hair follicles and different inflammatory infiltrates.[24–27,31]

3 | COMMONLY OCCURRING EGFR TKI-RELATED GASTROINTESTINAL AES

The squamous epithelium covering the tongue, esophagus and gastrointestinal tract can be affected by AEs caused by EGF deficiency.[32]

Gastrointestinal symptoms associated with EGFR TKI therapy such as oral complications and diarrhea will be discussed in this section of the review.

3.1 | Oral complications

Oral mucotitis and stomatitis are the most common EGFR TKI-related AEs affecting the mucous membrane of the gastrointestinal tract and oral cavity. A patient with oral mucositis may have extensive erythema or aphthous-like stomatitis.[20] Older patients and patients who have poor dental hygiene or uses dentures are more prone to develop these complications.[6] Majority of stomatitis/mucositis cases are mild, but can be very painful and make eating and drinking difficult for the patient.

3.2 | Diarrhea

EGFR TKIs-related diarrhea are caused by the presence of EGFR on epithelial cells, particularly the GI tract.[3] We refer to CTCAE v4.03 for the description of the various grades of diarrhea. Briefly, grade 1, 2 and 3 refers to the increase of less than 4, 4 to 6 and more than 7 stools per day over baseline, respectively. Table 1 describes the frequency of diarrhea between the various first and second generation EGFR TKIs. However, the mechanisms underlying diarrhea associated with EGFR TKI therapy remain poorly understood. It was proposed that excess chloride secretion during EGFR TKI treatment causes a secretory form of diarrhea.[33] Conversely, it was thought that EGFR TKI-associated diarrhea is caused by multiple factors, such as changes in gut motility; damage in the colonic crypt and altered intestinal microflora.[34] In our routine practice, we observed that afatinib induced diarrhea earlier during treatment compared to first generation EGFR TKI. More than half of our patients experience diarrhea within 2 to 3 days of therapy and around 70% of patients by 14 days.

3.3 | Managing EGFR TKI-related AEs

Patient education is an important element in managing AEs. Physicians should educate patients on how frequent and how intense specific AEs can be, as well as the consequences of delaying treatment. Optimal management of AEs are based on prophylaxis, which includes pre-emptive interventions that address frequently occurring toxicities, close patient monitoring, assessment of risk factors, early detection, severity grading and early intervention.

AEs in some patients may require a dose modification strategy in which the dose of TKIs is reduced/adjusted or discontinued; and then reintroduced at a lower dose once the AE improves to a lower grade. The dose reduction strategies are different among the various TKIs; and the management of AEs at various grades may be different according to the product information. A major concern for dose titration is that the drug could be less efficacious because of the suboptimal dosage. This issue was addressed in a combined post hoc analysis of the LUX-Lung 3, LUX-Lung 6[35] and LUX-Lung 7[36] studies, which showed that dose reduction of afatinib had limited effects on its efficacy. Patients whose dose was reduced within the first 6 months of treatment had similar median progression free survival (mPFS) as the cohort which remained on the indicated dose of 40 mg. Furthermore, a subgroup analysis of Japanese patients in the LUX-Lung 3 study demonstrated that patients could stay longer on treatment and receive clinical benefit if tolerability-guided dose adjustment of afatinib is practiced.[37]

The topical corticosteroids commonly used for skin-related AEs are desonide (DesOwen), betamethasone valerate (Betnovate) and fluticasone propionate (Cutivate). Examples of topical corticosteroid–antimicrobial combinations are betamethasone valerate and fusidic acid (Fucicort), betamethasone dipropionate (Diprolene) and gentamicin (Diprogenta) and betamethasone valerate and clioquinol (Demanol-C).

3.4 | Management of skin rash

The standard of care for managing rash includes topical and oral corticosteroids or antibiotics (lesions can be superinfected by bacteria). The management of EGFR-TKI induced skin toxicity is different between Caucasian and Asian population considering that the difference in skin sensitivity and higher likelihood of developing post-inflammatory hyper-pigmentation (PIH).[38] Table 2 summarizes the treatment options for each skin toxicity at various grades. For grade 1 rash, a topical anti-inflammatory antibiotic such as clindamycin 1% lotion bis in die (BD) usually suffices. A topical corticosteroid such as desonide 0.05% lotion BD may be added if it is itchy. For grade 2 rash, additional prednisolone may be considered to hasten recovery. Doxycycline 100 mg BD or minocycline 100 mg BD may be considered for 6–8 weeks to prevent another flare. Of note, in previously published EGFR-TKI AE consensus guidelines that focused on Caucasian patients, there was less emphasis on the use of oral steroids for EGFR-TKI induced skin toxicities.[5,6,39] As Asian patients are generally very disturbed by the consequence of PIH, in our guidelines, we have a lower threshold to use a short course of oral corticosteroids in order to more aggressively arrest the development of the AE from grade 2 and above.

If secondary bacterial infection is suspected (as evidenced by yellowish crusting, purulent discharge, increased skin pain), an anti-Staphylococcal antibiotic such as cloxacillin or cephalexin is recommended for a week before commencing secondary prophylaxis with doxycycline or minocycline. Also, the infected lesions can heal faster with potassium permanganate compresses for few days in addition to a topical corticosteroid-antimicrobial preparation. Grades 3 and 4 rashes should be comanaged with a dermatologist. Patients with grade 4 reactions may need attentive skin care and isolation to prevent secondary infections. Scalp rash may be managed using similar basic principles and recommendations. Scalp lesions can be treated with topical betamethasone valerate 0.1% lotion BD or mometasone furoate 0.1% lotion OD.[40] Tar-based shampoo or cetrimide wash are suitable treatment options.

The tetracycline antibiotics are thought to reduce the incidence of EGFR TKI-related skin rash without impacting efficacy through anti-inflammatory properties.[41] A systematic review and meta-analysis of 13 studies revealed 50% reduction in rash from all grade and

TABLE 2 Recommended management of various skin conditions in lung cancer patients receiving EGFR TKI-targeted therapies in Singapore

Condition	Grade	TKI administration decision	Treatments and interventions
Skin rash	1	Continue TKI at current dose	A topical anti-inflammatory antibiotics such as clindamycin 1% lotion BD should suffice. Topical corticosteroids may also be considered if itchy[a]
	2	Continue TKI at current dose/If intolerable, interrupt treatment	1. Oral anti-inflammatory antibiotic for at least 6 weeks (doxycycline 100 mg BD, minocycline 100 mg BD) 2. Clindamycin 1% lotion (Dalacin T) BD 3. Consider oral prednisolone 0.5 mg/kg/day for 5–7 days
	3	1. Interrupt TKI treatment 2. Consider referring to a dermatologist 3. Resume TKI at reduced dose if patient recovers to grade ≤2	As aboveIf infection is suspected (yellow crusts, purulent discharge or painful skin): • Anti-Staphylococcal antibiotic (cloxacillin 500 mg QDS, cephalexin 500 mg TDS) for 7 days • Consider skin swab for bacterial culture • Potassium permanganate washes and/or compress BD • Consider topical corticosteroid– antimicrobial combinations[b]
	4	1. Interrupt TKI treatment 2. Refer to a dermatologist (may need admission to dedicated skin/burn care unit)	
Xerosis and/or Pruritus	1	Continue TKI at current dose	Pruritus: Consider sedating antihistamines[c] and topical antipruritics eg menthol cream
			Xerosis: Moisturizing cream 200–300 g/week
	2	Continue TKI at current dose	Pruritus: As above + consider low to mid-potency topical corticosteroid[a]
			Xerosis: As above
	3	1. Interrupt TKI treatment; 2. Refer to a dermatologist. 3. Resume TKI at reduced dose if patient improves	Pruritus: As above
			GABA agonists, tricyclics, aprepitant[d]
			Xerosis: As above + bath oil
Paronychia	1	Continue TKI at current dose	• Topical potent corticosteroids[e] • Vinegar soaks (soaking fingers or toes in a solution of white vinegar in water 1:1 for 15 min every day) may be useful.
	2	Continue TKI at current dose	• Potent topical corticosteroids with/or without antimicrobials[f] • Silver nitrate applications to treat exuberant granulation tissue. • Refer to podiatrist/dermatologist for physical treatments. • Consider long-term prophylactic anti-inflammatory antibiotic eg doxycycline
	3	1. Interrupt TKI treatment 2. Refer to a dermatologist 3. Resume TKI at reduced dose if patient improves	As above

TKI, tyrosine kinase inhibitors.
For afatinib, it is recommended that treatment is interrupted for prolonged grade 2 (more than 7 days) or grade 3 skin reactions; treatment can subsequently be resumed with 10 mg dose reduction only when symptoms are fully resolved or improved to grade 1.
[a]Examples of topical corticosteroids (moderate/low strength): desonide 0.05% lotion/cream, betamethasone valerate 0.05% cream, fluticasone propionate 0.05% cream.
[b]Examples of topical corticosteroid-antimicrobial/antiseptic combinations: betamethasone valerate 0.1% + fusidic acid 1% cream (Fucicort), betamethasone valerate 0.1% + clioquinol.
[c]Examples of sedative antihistamines: hydroxyzine 25 mg t.i.d. [Be careful of fall risk in elderly patients who may suffer excessive daytime drowsiness.]
[d]Examples of GABA agonists (adjust if patient has renal impairment): gabapentin 300 mg every 8 h or pregabalin 50–75 mg every 8 h; examples of tricyclics: doxepin 25–50 mg every 8 h; aprepitant three doses: 125 mg on day 1, and 80 mg on days 2 and 3.
[e]Examples of topical corticosteroids (medium/potent strength): mometasone furoate 0.1% ointment, betamethasone valerate 0.1% ointment.
[f]Examples of potent corticosteroid–antimicrobial combinations: betamethasone dipropionate 0.05% + gentamicin (Diprogenta or Beprogenta) cream, betamethasone dipropionate 0.05% + Fucidin ointment.

70% reduction in severe grade rash, as well as a 40% reduction in paronychia.[42]

In terms of patient education, physicians should inform patients to avoid exposure to direct sunlight and wear protective clothes covering the head, face, hands, arms and legs.[43] In addition, a sunscreen with dual UVA/UVB protection should be generously applied at least four-hourly whenever exposure to the sun is a possibility (more frequent application may be necessary for patients who sweat excessively or during swimming). Sun protection becomes even more important if a tetracycline drug is prescribed as primary prophylaxis.

3.5 | Management of xerosis and/or pruritus

Patients who develop pruritus may benefit from topical, oral or systemic agents such as steroids, antihistamines or GABA agonists.[43] They can use hydroxyzine (50 mg) at night and a nonsedative antihistamine during the day.[6]

A suitable moisturizer should be used regularly to treat xerosis.[43] At least 200–300 g of moisturizer cream per week is highly recommended.[44] One review suggested using urea-free softening cream after showers and a medium strength corticoid.[6] The clinical management of xerosis and/or pruritus in Singapore is summarized in Table 2.

In terms of patient education, patient should be advised to use moisturizers to prevent dryness.[43] Soaps and detergents with strong scents should be avoided. Patients should be advised to bathe in cool or lukewarm water and to avoid long, hot showers. Sheets, clothing and undergarments should be washed using a mild detergent. Wool and other types of fabrics that can make the skin itch are best avoided; instead loose-fitting cotton clothing or other soft fabrics are recommended for regular wear. As dry air can dehydrate the skin, a humidifier can be considered indoors. Cold compresses can be directly applied over itchy areas for comfort.

3.6 | Management of paronychia

Patients with paronychia can benefit from topical antibiotics/antiseptics and silver nitrate. Grade 1 reactions may be treated with a potent corticosteroid such as betamethasone valerate 0.1% ointment (Betnovate or Dermasone) BD twice a day. Grades 2 and 3 reaction may benefit from potent topical corticosteroid–antimicrobial combinations. If there is exuberant granulation tissue not responding to silver nitrate applications (20%), refer to a dermatologist for physical measures such as electrodesiccation or carbon dioxide laser ablation. Long-term secondary prophylaxis with doxycycline is recommended. Partial or whole nail avulsion may be performed for cases of painful ingrowth of nail into granulation tissue. The clinical management of paronychia in Singapore is summarized in Table 2.

In terms of patient education, patient should be advised against biting and traumatizing their nails, aggressive manicures/pedicures as well as contact with irritating substances.[43,45,46] Prolonged exposure to water should also be avoided. If the patient has to wear vinyl gloves, they should use cotton gloves underneath. High-risk patients (diabetics/immunosuppressed patients) and patients repeatedly exposed to moist environments (housekeepers, swimmers, etc.) should take extra precautions to ensure their nails are dry and clean.

3.7 | Management of stomatitis/mucositis

Prophylactic treatment of stomatitis / mucositis is highly recommended. There are no conclusive data evaluating treatment for these conditions, but experts recommend advising patients with general mouth sensitivity to gargle with a benzydamine rinse.[5] Triamcinolone in dental paste can be used for grade 1 stomatitis / mucositis. For grade 2, oral erythromycin or minocycline should be added.[5] For grade 3, triamcinolone should be substituted with clobetasol ointment and the dose of oral erythromycin/minocycline should be increased.

Patients should be educated on dental hygiene and food. They should see a dental surgeon before treatment is initiated to diagnose and manage all infections or denture problems, except for removing tartar.[43]

In terms of patient education, patients should be advised to care for their oral health by using a brush with soft bristles, sodium bicarbonate and alcohol-free mouthwash; taking special care of dentures as they can cause oral sores.[47,48] Food should be consumed cold or at room temperature, and food that is acidic, spicy, salty or coarse should be avoided. Patients should drink a lot of water, preferably using a straw to sip liquids. Dry lips should be managed using a lip balm or petroleum jelly. Whenever needed, patients can numb the mouth with ice chips or flavored ice pops.

3.8 | Management of diarrhea

Loperamide is considered the mainstay pharmacologic treatment for diarrhea; with doses escalated to the highest recommended approved dose as needed.[49] Loperamide, a synthetic oral opioid drug, prolongs the transit time of intestinal contents, decreases daily fecal volume and improves its viscosity and bulk density, as well as diminishes the loss of fluid and electrolytes. Treating physicians should closely follow-up with patients approximately 3 days after the initiation of EGFR TKI therapy.

As with dermatological AEs, each EGFR TKI has specific instructions on dose reduction to overcome drug-induced diarrhea. The following describes the common dose reduction practices for patients prescribed afatinib, which is known to induce diarrhea early (i.e. within 2 to 3 days of application); In the event of grade 1–2 diarrhea, patients should start immediate treatment with loperamide (two tablets = 4 mg) and continue taking one tablet after each episode (up to 16 mg/day) until there are no bowel movements for 12 h. EGFR TKI treatment should be continued at the same dose. If grade 2 diarrhea persists for more than 48 h despite antidiarrheal treatment, afatinib interruption is recommended. Afatinib can be recommenced at a reduced 10 mg/day dose after diarrhea symptoms have resolved to grade $\leq$1. Loperamide treatment should be continued and patients should be assessed for dehydration and electrolyte imbalance. Intravenous fluids therapy and electrolyte replacement should be

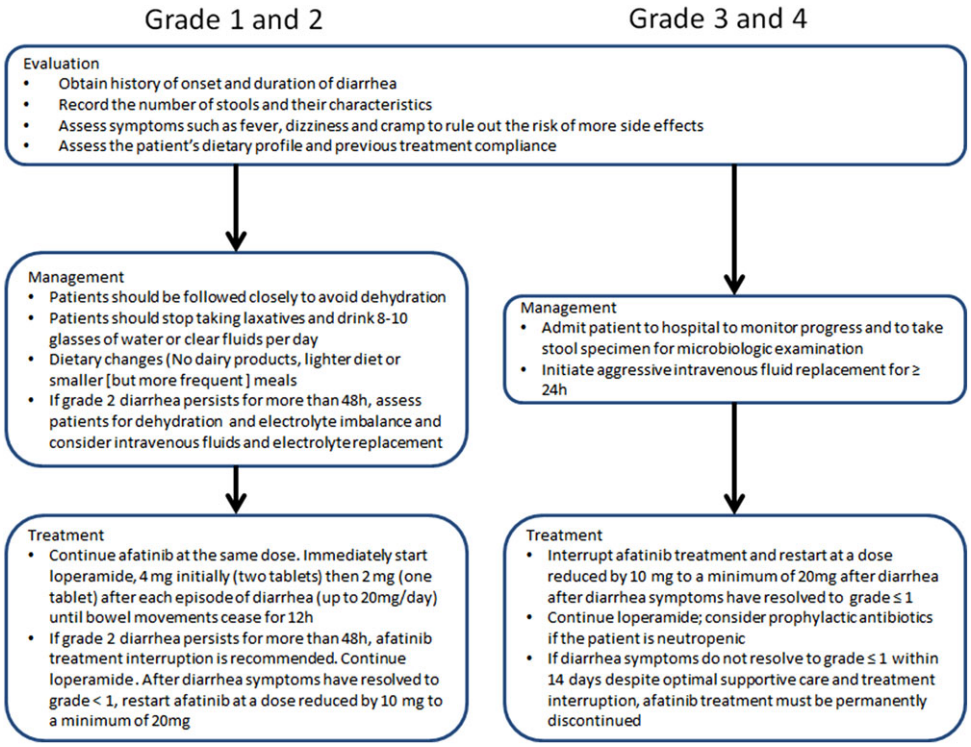

FIGURE 4 Algorithm for the management of grades 1–4 diarrhea associated with EGFR TKI therapy. EGFR TKI, Epidermal growth factor receptor tyrosine kinase inhibitor. [Colour figure can be viewed at wileyonlinelibrary.com]

considered (Figure 4). In the event of grade 3 or 4 diarrhea, the patient should be admitted to the hospital and aggressive intravenous fluid replacement should be initiated. Patients should continue to receive loperamide treatment, although prophylactic antibiotics can be considered if the patient has neutropenia. EGFR TKI treatment must be interrupted, but can be recommenced at a reduced 10 mg/day dose after diarrhea symptoms have resolved. With these measures, symptoms should improve to grade ≤1 by 14 days. If improvements are not seen, afatinib treatment must be ceased permanently.

Certain risk factors have been linked with a higher incidence of grade 3 diarrhea in afatinib-treated patients starting afatinib dose of 50 mg/day. These include a low (<50 kg) bodyweight, female gender and baseline renal impairment (creatinine clearance ≤80 mL/min). These factors may be useful in predicting the development of diarrhea. However, these observations are based on small patient numbers and should be confirmed in larger sample sizes. Although early and appropriate treatment for afatinib-associated diarrhea appears to be essential, data to support the routine implementation of prophylactic treatment is still inconclusive. Management strategies to reduce the severity, or eliminate diarrhea entirely, are advocated to avoid reducing the dose of afatinib or the need to change the regimen if a clinical response is likely.[37]

4 | CONCLUSION

The EGFR TKIs has changed the treatment paradigm for advanced NSCLC, providing patients with better efficacy and quality of life than chemotherapy. The EGFR TKIs also have favorable toxicity profiles, but prolonged use may impact patients' quality of life, treatment compliance and ultimately clinical outcome. The most common AEs for EGFR TKIs are cutaneous (rash, xerosis, paronychia and scalp lesions) and gastrointestinal related (oral complications and diarrhea), because EGFR is mainly expressed in epithelial cells. Importantly, optimize supportive measures by pre-empting AEs, dose modifications strategies which vary with TKIs and by AE grades, individualized proactive/early intervention and appropriate education for both patients and physicians.

A "third-generation" EGFR TKI group known as wild-type EGFR sparing inhibitors may provide an alternative option in the future.[50] Trials to determine if this novel class of EGFR TKIs are indicated in the first-line setting are ongoing.

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AUTHORS' CONTRIBUTIONS

Ross Soo conceived and designed this review. All authors were involved in preparing the manuscript and its final approval.

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