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BEST PRACTICES for Managing EGFR Tyrosine Kinase Inhibitor–Related Adverse Events

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Overview of EGFR Tyrosine Kinase Inhibitors

Currently approved EGFR tyrosine kinase inhibitors (TKIs) are classified as being first-, second-, or third-generation agents. First-generation TKIs (erlotinib, gefitinib) bind to different EGFR-related targets and/or mutations reversibly; however, acquired resistance to the agent may develop. Second-generation TKIs (afatinib, dacomitinib) and third-generation TKIs (osimertinib, mobocertinib) bind irreversibly and more selectively to EGFR to combat this resistance.[1,2]

Common Adverse Events With EGFR TKI Therapy

Due to the high expression of epidermal growth factor on healthy cells, especially those of epithelial origin (eg, gastrointestinal tract, liver, and skin), toxicities often express as skin manifestations (eg, rash, paronychia) and diarrhea.[3] Inflammation of the skin, hair follicles, and scalp likely result from disruption of cell proliferation upon binding of TKIs to EGFR, whereas diarrhea results from excessive chloride secretion. Common adverse events (AEs) noted with TKI use are presented in **Table 1**.[4-9]

Management Of Common Adverse Events Associated With TKIs

Implementation of proactive patient education on AEs and a multidisciplinary approach are important for preventing and ameliorating toxicities. The oncology care team—ideally composed of doctors, midlevel specialty clinicians, and clinical pharmacists—should ask the patient about use of current prescriptions or OTC medications, vitamins, or supplements to minimize the risk of interactions that may interfere with TKI treatment.

Skin Rash

Skin rashes are graded as mild, moderate, or severe according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) rubric, as described in **Table 2**.[3,10-12]

The recommended intervention for grade 1 rash is continued TKI therapy while monitoring for changes in severity; skin reactions may be treated with a topical steroid and/or a topical antibiotic.[3,11,12] After 2 weeks, if the rash worsens to grade 2 severity or does not improve, TKI therapy may be resumed; treatment should include topical hydrocortisone, clindamycin, or pimecrolimus (1% cream) with the addition »

Table 1. Common Adverse Events Associated With EGFR TKIs[4-9]

Adverse event	Erlotinib	Gefitinib	Afatinib	Dacomitinib	Osimertinib	Mobocertinib
Rash, %	60-85	47	70-90	69-78	34-58	78
Paronychia, %	14	—	11-58	13-64	—	> 20
Diarrhea, %	20-62	29	75-96	87	41-58	93
Fatigue, %	52	—	—	9	13-22	29
Cardiovascular, %	—	—	—	—	≤10	10

Table 2. Management of EGFR TKI-associated Skin Rash[3,10-12]

Grade (CTCAE)	Characteristics	Management Strategies
Grade 1 (mild)	Affects < 10% BSA, minimal symptoms, no ADL effects, no superinfection	Continue TKI at current dosing; initiate use of topical hydrocortisone (1% or 2.5% cream) and/or clindamycin (1% gel).
Grade 2 (moderate)	Affects 10%-30% BSA, pruritis, tenderness, minimal ADL effects, no superinfection	Continue TKI at current dosing; initiate use of topical hydrocortisone, clindamycin, or pimecrolimus (1% cream) *and* oral doxycycline or minocycline.
≥ Grade 3 (severe)	Affects > 30% BSA, symptoms affect ADL, potential for superinfection	Reduce TKI dose per label recommendations (dose interruptions or discontinuation may be needed); continue use of topical agents and oral antibiotics, and initiate oral steroids.

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

of an anti-inflammatory oral antibiotic. If symptoms do not improve or worsen to grade 3 or greater after 2 weeks, continue topical therapy, add oral steroids, and reduce the TKI dose according to the label instructions. In cases where reactions have worsened at reassessment (2 weeks), dose interruption or treatment discontinuation may be needed. For facial rashes, a low-potency topical steroid (eg, hydrocortisone 2.5% or less) is preferred to avoid steroid-related AEs; topical clindamycin may also be useful. Scalp rashes can be problematic, but may respond well to minimal hair washing, use of clobetasol and/or ketoconazole shampoo, doxycycline, and oral isotretinoin. Mouth sores are best treated with salt water, "miracle" or dexamethasone mouthwash, and a rinse of combining baking soda and saltwater, especially after eating and before going to bed. Patients should moisturize their lips frequently to avoid drying out from these rinses. Triamcinolone dental paste or viscous lidocaine may also be applied directly to lesions; triamcinolone dental paste or viscous lidocaine may also be applied directly to lesions. Associated hair loss has responded well to minoxidil.

Paronychia

Paronychia, defined as an infectious process involving the soft tissues around the nail, is likewise classified in stages of severity according to CTCAE criteria (**Table 3**).[10,13]

Patients taking EGFR TKIs should contact their health care provider as soon as nail problems emerge, as symptoms can escalate quickly. Recommended interventions for mild, grade 1 nail toxicity include topical steroids, antiseptics, and warm water or diluted white vinegar soaks while continuing the TKI

Table 3. Management of EGFR TKI-associated Paronychia[10,13]

Grade (CTCAE)	Characteristics	Management strategies
Grade 1 (mild)	Cuticle disruption or nail fold edema/erythema	Continue TKI at current dosing; initiate very potent topical steroids (eg, clobetasol), antiseptics, antifungals, and antibiotics. Warm water or vinegar plus white vinegar soaks (1:1 ratio) for 15 min 3-4 times/d may be used.
Grade 2 (moderate)	Discharge from nail or nail plate separation	Dose reduction or interruption may be needed; initiate oral antibiotics, and consider use of silver nitrate if overgranulation is present.
≥ Grade 3 (severe)	Nail avulsion	Withhold TKI; consider initiating IV antibiotics and/or operative interventions. Use of the TKI should only be resumed when AE symptoms have resolved to ≤ grade 2.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; TKI, tyrosine kinase inhibitor.

at its current dose.[13] Other treatment options for paronychia may include the application of tea tree oil, diluted bleach soaks, or topical mupirocin. Referral to a dermatologist and/or podiatrist for further assessment and treatment is recommended at this or any stage of paronychia. Nail avulsions performed by a dermatologist or podiatrist may help in severe cases of nail separation. With grade 2 toxicity, the addition of oral antibiotics and more potent topical corticosteroids (eg, clobetasol) is recommended along with possible dose reduction or interruption of the TKI until paronychia resolves. Silver nitrate may be considered in cases involving overgranulation. If grade 3 paronychia is present, abscess drainage and/or wound swab and culture is recommended along with considerations for IV antibiotics and operative intervention. The TKI should be discontinued and only reinstated when the paronychia resolves to at least grade 2 or lower.

Diarrhea

TKI-induced diarrhea commonly occurs within the first 4 weeks of treatment; it is graded according to CTCAE criteria (**Table 4**).[10,14]

Patient education is important before treatment initiation, and careful monitoring and management of electrolyte status is essential during treatment of diarrhea. Patients should be given anticipatory guidance about diarrhea management, making sure they have the tools on hand to manage it, and that they know when to call their doctors. Diarrhea often occurs within the first 4 weeks after treatment; however, patients can experience issues as soon as 1 week following treatment initiation. As such, timely follow-up appointments are important to the management of diarrhea. A baseline frequency of daily bowel movement is important and patients should contact their provider when they experience more than 4 consecutive loose stools or 3 to 4 events over baseline, and a thorough evaluation of the patient's medication, diet modification, and loperamide may be indicated. Mild grade 1 diarrhea calls for dosing of loperamide 4 mg at onset and up to 2 mg every 2 hours (maximum dose, 20 mg/d) until 12 hours have passed without a bowel movement; the TKI may be maintained at the current dose.[14]

For persistent or grade 2 diarrhea, loperamide should be continued, and the possibility of dehydration and electrolyte imbalances should be assessed; administration of diphenoxylate-atropine or tincture of opium may be considered as an alternative to loperamide. If there is no response after 48 hours, TKI treatment should be temporarily discontinued until symptoms resolve to grade 1 or less; it may be resumed according to package insert guidelines.

Severe (grade 3-4) diarrhea calls for hospital admission with aggressive IV fluid replacement as well as laboratory studies, including stool culture to rule out *Clostridiodes difficile* infection. Prophylactic antibiotics should be administered. Continue to hold the TKI; depending on the grade of severity and the agent used, resumption may be possible. Although octreotide can be helpful in managing severe, refractory, TKI-induced diarrhea, faculty noted that it is rarely needed in the majority of cases.

Additional Toxicities of Note With EGFR TKIs

The prescribing information for EGFR TKIs carries a boxed warning concerning prolongation of the corrected »

Table 4. Management of EGFR TKI-associated Diarrhea[10,14]

Grade (CTCAE)	Characteristics	Management strategies
Grade 1 (mild)	< 4 stools/d over baseline	Continue TKI at current dosing; initiate loperamide 4 mg at onset and 2 mg after each subsequent stool (maximum dosage, 20 mg/d)
Grade 2 (moderate)	4-6 stools/d over baseline	Continue loperamide or consider alternative therapy with diphenoxylate-atropine or codeine; if no response is noted after 48 h, discontinue TKI and reinitiate per label recommendations and after symptoms resolve to ≤ grade 1.
≥ Grade 3 (severe)	≥ 7 stools/d over baseline	Discontinue TKI; admit patient to a hospital, and institute aggressive IV fluid replacement; administer prophylactic antibiotics; rule out *Clostridiodes difficile* infection; reinitiate TKI after considering grade of severity and TKI.

CTCAE, Common Terminology Criteria for Adverse Events; TKI, tyrosine kinase inhibitor.

Table 5. Management of QTc Prolongation With Mobocertinib[9]

Grade	Characteristics	Management strategies
Grade 1 (mild)	Asymptomatic	—
Grade 2 (moderate)	QTc of 481-500 msec	Hold mobocertinib until QTc returns to baseline; reinitiate therapy at the same dose. For repeat episodes, dose reduction is recommended.
Grade 3 (severe)	QTc ≥ 501 msec or > 60 msec from baseline	Hold mobocertinib; urgent intervention is indicated. Therapy may be reinitiated at a reduced dose; for repeat episodes, treatment discontinuation is recommended.
Grade 4 (severe)	Torsades de pointes, polymorphic ventricular tachycardia, other serious arrhythmias	Treatment discontinuation is warranted.

QTc, corrected QT interval.

QT-interval (QTc) and torsades de pointes; warnings and precautions for interstitial lung disease (ILD)/pneumonitis, and/or cardiac toxicities are also featured.[9] Antiemetics given 30 to 60 minutes before doses of mobocertinib can help alleviate nausea and combat diarrhea symptoms.

QTc Interval Prolongation

Cardiac AEs with mobocertinib may manifest as heart palpitations, shortness of breath, lightheadedness, syncope, or chest pain; symptoms should be assessed by EKG performed at symptom onset and intermittently, along with electrolyte studies and a review of medications.[9] **Table 5** provides an overview of management strategies for QTc prolongation.[9]

Upon the first occurrence of grade 2 QTc prolongation, mobocertinib should be held until the patient returns to baseline or is asymptomatic; upon recovery, mobocertinib therapy may be resumed at the same dose.[9] Subsequent recurrences are treated similarly; however, the TKI should be resumed at the next lower dose upon recovery. Grade 3 toxicity requires urgent intervention and immediate withholding of the drug until recovery and then resumed at the next lower dose. Permanent treatment discontinuation is warranted in cases of recurrent episodes or life-threatening grade 4 toxicities.

ILD/Pneumonitis

ILD and pneumonitis can manifest with dyspnea, dry cough, wheezing, tachypnea, hypoxia, fever or increased oxygen requirements in patients receiving supplemental oxygen. Preventive strategies include recommendations for smoking cessation and vaccinations.[9] Oxygen saturation should be measured at rest and during ambulation before starting therapy and regularly thereafter. If lung involvement is suspected, a chest CT is warranted to rule out other causes. When lung involvement is confirmed, oxygen support, antibiotic administration, infectious disease consultation, and inpatient care may be necessary. Mobocertinib should be withheld if ILD/pneumonitis is suspected and permanently discontinued when confirmed.

Looking Ahead

Faculty agreed that a collaborative approach to patient care is crucial in providing optimal patient outcomes with the use of EGFR TKIs. Anecdotal patient remedies have been successful in some cases, and may be helpful to share with other patients. It is important to educate patients regarding common TKI-related AEs and potential dose reductions or holds that may be needed during the course of treatment. Dose modifications are especially common during the first 4 to 6 weeks of treatment; therefore, it is important to determine optimal dosing for patients before treatment initiation to ensure long-term adherence and therapeutic success. Sharing resources with colleagues and patients can be helpful in optimizing treatment outcomes; patient education sheets with helpful recommendations may also be beneficial. ■

References are available on OncLive.com.