



Management of diarrhea induced by epidermal growth factor receptor tyrosine kinase inhibitors

V. Hirsh MD,* N. Blais MD MSc,[†]
R. Burkes MD,[‡] S. Verma MD,[§] and
K. Croitoru MDCM^{||}

ABSTRACT

Treatment for non-small-cell lung cancer (NSCLC) is moving away from traditional chemotherapy toward personalized medicine. The reversible tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib were developed to target the epidermal growth factor receptor (EGFR). Afatinib, an irreversible ErbB family blocker, was developed to block EGFR (ErbB1), human epidermal growth factor receptor 2 (ErbB2), and ErbB4 signalling, and transphosphorylation of ErbB3. All of the foregoing agents are efficacious in treating NSCLC, and their adverse event profile is different from that of chemotherapy. Two of the most common adverse events with EGFR TKIs are rash and diarrhea. Here, we focus on diarrhea. The key to successful management of diarrhea is to treat early and aggressively using patient education, diet, and antidiarrheal medications such as loperamide. We also present strategies for the effective assessment and management of EGFR TKI-induced diarrhea.

KEY WORDS

Non-small-cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitors, adverse events, diarrhea management

1. INTRODUCTION

Non-small-cell lung cancer (NSCLC), with its three main histologic subtypes, adenocarcinoma, squamous cell carcinoma, and large cell anaplastic carcinoma, accounts for approximately 85% of all lung cancers^{1,2}. The heterogeneous histologies of NSCLC have traditionally been grouped because of similarities in treatment and prognosis; however, evidence shows that they can respond differently to treatment³.

Most patients with NSCLC receive chemotherapy as first-line treatment. However, in NSCLC patients with either an *EGFR* mutation (10%–15% of white⁴ and 20%–40% of Asian⁵ NSCLC patients) or an *ALK*

mutation (3%–5% of NSCLC patients)^{6,7}, the approach to treatment is moving toward targeted agents. Although many such patients will ultimately receive chemotherapy, targeted agents allow for a personalized approach to treatment through identification of the presence of gene profiles or disease-specific genes that control cancer growth.

With respect to the epidermal growth factor receptor (EGFR), tyrosine kinase inhibitors (TKIs) have been developed that impede phosphorylation of its intracellular tyrosine kinase component, blocking downstream signalling pathways associated with the proliferation and survival of cancer cells^{8,9}. For patients with *EGFR* mutation-positive NSCLC, EGFR TKIs are an effective treatment, especially in the first-line setting^{10–12}. However, because of further mutations such as the T790M mutation in exon 20 of the tyrosine kinase domain of EGFR, amplification of the *MET* proto-oncogene, or other mechanisms, patients almost invariably develop resistance to EGFR TKIs^{13–15}.

The reversible EGFR TKIs erlotinib and gefitinib compete reversibly with ATP for the ATP binding site of the intracellular kinase domain of the EGFR receptor¹⁶. The irreversible EGFR TKIs, such as afatinib and dacomitinib, were developed to overcome resistance to the reversible EGFR TKIs by binding irreversibly to the active site of the kinase domain of EGFR¹⁶. They also simultaneously inhibit multiple ErbB receptors and oncogenic pathways. For example, afatinib is an ErbB family blocker that blocks EGFR (ErbB1), human epidermal growth factor receptor 2 (ErbB2), and ErbB4 signalling, and transphosphorylation of ErbB3^{17,18}. Adverse events (AEs) with the EGFR TKIs are different from those with chemotherapy, the most frequent and manageable being rash and diarrhea⁸.

2. EGFR TKI-INDUCED DIARRHEA

Diarrhea induced by EGFR TKIs is most likely to occur in the first 4 weeks after treatment initiation^{19,20}; diarrhea induced by afatinib is most likely to occur within the first 7 days²¹. This type of diarrhea is thought

to be primarily secretory, although the mechanism remains unclear^{22,23}.

Several possible mechanisms for EGFR TKI-induced diarrhea have been postulated. One theory proposes that, in normal gastrointestinal mucosa, EGFR, a negative regulator of chloride secretion, is often overexpressed²³. The EGFR TKIs might block that regulation pathway, increasing chloride secretion, which would induce secretory diarrhea^{23,24}. An alternative theory is that the EGFR TKIs inhibit EGFR signalling, leading to a reduction in growth and impaired healing of the intestinal epithelium where EGFR is expressed, subsequently causing mucosal atrophy²⁵. It has also been suggested that a combination of factors cause EGFR TKI-induced diarrhea, including altered gut motility, colonic crypt damage, changes in the intestinal microflora, and altered colonic transport²¹. Finally, data from the Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) trial showed that patients using a prophylactic skin treatment regimen that included oral doxycycline 100 mg twice daily were less likely than patients on a reactive skin treatment regimen to experience any grade of diarrhea (56% and 85% respectively)²⁶. Doxycycline could be acting as an anti-inflammatory or an antimicrobial agent, suppressing diarrhea caused by the EGFR inhibitor panitumumab, suggesting that an inflammatory or infectious component might be involved.

3. ASSESSMENT AND GRADING

The guideline most commonly used to determine the severity of diarrhea is the *Common Terminology Criteria for Adverse Events* from the U.S. National Cancer Institute (Table 1)²⁷. The AE grades are determined in part by the increase in the number of stools per day over baseline: grade 1 is an increase of less than 4 stools, grade 2 is an increase of 4–6 stools,

TABLE 1 Severity of diarrhea by grade

Grade	CTCAE description
1 Mild	Increase of fewer than 4 stools per day over baseline
2 Moderate	Increase of 4–6 stools per day over baseline
3 Severe	Increase of 7 or more stools per day over baseline; incontinence; hospitalization indicated; limits self-care activities of daily living
4 Life-threatening	Life-threatening consequences; urgent intervention indicated
5 Death	Death

CTCAE = *Common Terminology Criteria for Adverse Events* (version 4.03)²⁷.

and grade 3 is an increase of 7 or more stools. In addition, grade 3 includes incontinence limiting self-care activities of daily living, with hospitalization indicated. Grade 4 is considered life-threatening with urgent intervention indicated, and grade 5 is death.

However, using the *Common Terminology Criteria for Adverse Events* alone is not sufficient to provide a complete assessment. During evaluation of the patient, additional information should be gathered, including stool characteristics and coexisting symptoms and their duration²⁸.

In addition, causes of diarrhea other than the EGFR TKI should be ruled out. Other potential causes of diarrhea include medications (stool softeners, antacids, laxatives, antibiotics), diet intolerances (lactose, for instance), radiation toxicity, surgeries (short bowel syndrome or gastrectomy), fecal impaction, intestinal obstruction, and comorbid infections. Laboratory tests can rule out some causes of diarrhea: neutropenia can be detected from a complete blood count and differential, renal function and electrolyte abnormalities can be assessed using blood tests, and bacterial pathogens can be checked through a stool culture or *Clostridium difficile* toxin screen. To rule out coexisting disorders such as bowel ischemia, perforation, or obstruction, evaluation with abdominal radiography or endoscopy and biopsy can be performed^{8,28,29}.

4. INCIDENCE OF DIARRHEA

In phase III clinical trials involving EGFR TKIs, the incidence of diarrhea varied substantially by drug and dosage given (Table II). In the trials, the incidence of diarrhea ranged from 18% to 95%, with up to 25% of patients experiencing grade 3 or higher diarrhea.

Interestingly, the incidence of grade 3 diarrhea in the LUX-Lung 3 trial, which compared afatinib with chemotherapy, was 14.4% for patients who received afatinib⁶⁰. However, in the LUX-Lung 6 trial, which was completed after the LUX-Lung 3 trial, the incidence of grade 3 diarrhea was 5.4% for patients who received afatinib—a substantial difference⁶⁷. The main differences in these trials were the type of chemotherapy given (which would not affect the AE profile of patients in the afatinib arm) and the ethnic origin of the patient population. The LUX-Lung 6 trial had an all-Asian population; the ethnicity of the patient population in LUX-Lung 3 was 72% eastern Asian, 26% white, and 2% other. The difference in severe diarrhea had been speculated to be a result of the difference in the ethnicities of the study populations. However, a recent analysis comparing the incidence of diarrhea in the two trials by ethnicity showed comparable results between the groups (grade 3 diarrhea occurred in 9.7% of the Asian patients and in 10.9% of the non-Asian patients)⁶⁸. The treatment protocols for diarrhea were consistent across the two trials, but the heightened awareness of the importance of

TABLE II Incidence of diarrhea with epidermal growth factor receptor tyrosine kinase inhibitors from selected clinical trials in non-small-cell lung cancer^a

Tyrosine kinase inhibitor	Grade (%) of diarrhea	
	All	≥3
Erlotinib 150 mg		
All studies	10–69	0–17
Phase III studies	18–68	1–12
Gefitinib 250 mg and 500 mg		
All studies	27–75	0–25
250 mg	27–58	0–10
500 mg	51–75	5–25
Phase III studies	27–69	1–25
250 mg	27–58	1–10
500 mg	51–69	12–25
Afatinib 40 mg and 50 mg		
All studies	67–100	0–37
40 mg	67–97	0–14
50 mg	87–100	17–37
Phase III studies	87–95	5–17
40 mg	88–95	5–14
50 mg	87	17
Dacomitinib 15 mg, 30 mg, and 45 mg		
All studies (phase II)	77–97	0–15
30 mg	77	0
45 mg	81–97	13–15

^a Adapted and updated from Hirsh 2011^{8–12,30–66}.

treating diarrhea early might have been the reason that the incidence of high-grade events dropped in the LUX-Lung 6 trial. In addition, the oncologists in the LUX-Lung 3 trial were less experienced at treating EGFR TKI-induced diarrhea because of the small number of patients (1–3 patients) in some centres.

5. IMPACT OF DIARRHEA

Diarrhea can cause discomfort, fatigue, and sleep disturbance, and can affect social functioning because patients are reluctant to leave the house. Alterations in gastrointestinal transit and digestion can lead to nutritional deficiencies that can negatively affect quality of life. Severe diarrhea can result in fluid and electrolyte loss, which can lead to dehydration, electrolyte imbalances, and renal insufficiency²⁸. Notably, although most clinical trial results do not report moderate diarrhea (grade 2) as a separate category (they usually report all grades and grades 3 and 4), in our expert opinion, grade 2 diarrhea is not inconsequential and can have a significant effect on quality of life.

Although diarrhea can have a profound effect on patients, available evidence suggests that diarrhea is

an indicator that EGFR TKIs are working effectively. In a retrospective study of patients with NSCLC treated with gefitinib on the Expanded Access Program at the MD Anderson Cancer Center, univariate and multivariate analyses were used to determine relationships between patient characteristics and treatment outcomes. Among patients who received gefitinib 250 mg, the presence of diarrhea was identified as one of the independent predictors of a partial response, and the absence of diarrhea was one of the predictors of progressive disease⁶⁹. A study of EGFR TKIs that included data from phase II clinical trials of gefitinib and erlotinib in patients with recurrent and metastatic squamous cell carcinoma of the head and neck showed a similar association between EGFR TKI-induced diarrhea and clinical benefit and also an association with more favourable overall survival⁷⁰. Finally, combined AE data from the LUX-Lung 3 and LUX-Lung 6 trials comparing afatinib with chemotherapy in patients with EGFR mutation-positive NSCLC showed a trend toward a higher rate of progression-free survival in patients who had grade 2 or greater diarrhea in the first 28 days of treatment with afatinib (compared with patients who experienced no AEs); however, no statistically significant differences were observed⁶⁵.

6. MANAGEMENT

Diarrhea associated with taking an EGFR TKI usually ranges from mild (grade 1) to moderate (grade 2). Dietary changes and antidiarrheal medications are usually sufficient to control diarrhea^{8,28,29,71}. However, to avoid escalation of symptoms and to prevent dose reduction or discontinuation of the EGFR TKI, it is critical to manage symptoms and fluid intake early. Management of EGFR TKI-induced diarrhea is identical to management of chemotherapy-induced diarrhea and includes patient education and both nonpharmacologic and pharmacologic management strategies.

6.1 Education and Nonpharmacologic Management Strategies

Patient education should ideally begin before treatment and continue throughout treatment. Patients should be advised to discuss with the health care team any symptoms of diarrhea as soon as they occur. It is critical that patients understand the importance of managing symptoms early and aggressively to avoid EGFR TKI discontinuation, which has negative consequences. For the first 4 weeks of treatment, a nurse familiar with EGFR TKI-induced diarrhea should be assigned to speak with the patient every week, in person or on the telephone, to monitor AEs that might occur.

Patients should also be advised of nonpharmacologic management strategies, which include dietary change, fluid intake, and probiotics. A patient

who experiences diarrhea should adopt the BRAT diet (bananas, rice, applesauce, toast) and should eliminate greasy, spicy, and fried foods that can make symptoms worse and also cruciferous vegetables that can increase bloating and abdominal cramping. For approximately 1 week after the patient experiences diarrhea, milk products should also be avoided because of the temporary lactose intolerance caused by the decrease in lactase activity that can occur with epithelial damage. Dietary changes are not recommended in anticipation of diarrhea—that is, prophylactically. Once symptoms improve, the patient can introduce foods such as eggs, pasta, and skinless chicken if tolerated^{8,28,29,71}. In addition to dietary changes, patients should drink 3–4 L of fluid daily to prevent dehydration. To avoid hyponatremia or hypokalemia from loss of electrolytes, some of the fluid intake should include sugar or salt²¹.

There is some evidence that supplementation with probiotics might reduce the severity of chemotherapy-induced diarrhea and abdominal discomfort, with few or no AES⁷². In a study by Österlund *et al.*, *Lactobacillus* supplementation reduced the frequency of grades 3 and 4 diarrhea⁷³. Compared with patients in the control arm of the study, patients who received supplementation with *Lactobacillus* during chemotherapy also reported less abdominal discomfort and had fewer chemotherapy dose reductions⁷³, findings that might potentially apply to EGFR TKI-induced diarrhea. However, no clinical trials have specifically evaluated the role of probiotics in diarrhea caused by EGFR TKIS.

6.2 Pharmacologic Management Strategies

Pharmacologic management of EGFR TKI-induced diarrhea is based on the grade of diarrhea experienced (Table III) and is usually limited to loperamide. No antidiarrheal medication is taken prophylactically because constipation is a risk, especially if the patient is already taking narcotics for pain management, and because not all patients will develop diarrhea. Should diarrhea arise, the patient's current medication should be reviewed, with an emphasis on the removal of stool softeners and laxatives.

Before patients initiate EGFR TKI therapy, they should be prescribed an antidiarrheal agent such as loperamide and be advised to start taking it immediately upon onset of diarrhea. For mild (grade 1) diarrhea, the patient should take 4 mg (2 tablets) of loperamide immediately after symptoms begin and then 2 mg (1 tablet) after each loose stool to a maximum of 20 mg daily until 12 hours have passed with no episodes of diarrhea. If diarrhea persists or becomes moderate (grade 2), the patient should continue with loperamide (to a maximum of 20 mg daily, as for grade 1) and be assessed for dehydration and electrolyte imbalances. If the diarrhea reaches grade 3 or 4, the patient should be hospitalized. At

that point, loperamide should be continued, and aggressive intravenous fluid replacement should be initiated. In addition, infection should be ruled out by stool culture, and if the patient is neutropenic, antibiotics should be given prophylactically^{8,21}. Although it might not be necessary for the oncologist to consult with a gastroenterologist on an outpatient basis to manage a patient's diarrhea, a gastroenterologist might be consulted once a patient is admitted to hospital, especially if an endoscopic evaluation is required.

Alternatives to loperamide are diphenoxylate-atropine and codeine, either of which can be used with loperamide. Patients should take 5 mg (2 tablets) of diphenoxylate-atropine 4 times daily (maximum of 20 mg daily) or 30 mg codeine every 4 hours²⁹.

The dose of the EGFR TKI should be maintained in the presence of grade 1 diarrhea. At grade 2, if the patient does not respond to loperamide after 48 hours, the EGFR TKI should be temporarily discontinued until the diarrhea returns to grade 1, at which time the EGFR TKI should be resumed using these guidelines:

- Lower the afatinib dose by 10 mg at a time to a minimum dose of 20 mg.
- Lower the erlotinib dose by 50 mg at a time to a minimum dose of 50 mg (no sufficient data on efficacy are available in the literature).
- Resume gefitinib only at the original dose (the dose of gefitinib cannot be lowered and no data on its efficacy with a modified schedule are available)^{8,21}.

For grade 3 or 4 diarrhea, the EGFR TKI should be withheld until diarrhea reaches grade 1, after which the EGFR TKI should be resumed using the guidelines already stated. The EGFR TKI should be permanently discontinued if diarrhea does not reach grade 1 within 14 days despite best supportive care and withholding of the TKI^{7,20}.

Earlier algorithms have suggested the use of octreotide if dose reduction or discontinuation of the EGFR TKI was ineffective⁸, but in practice, the need for octreotide is extremely rare, and no direct clinical study supports the efficacy of octreotide in EGFR TKI-induced diarrhea.

7. SUMMARY

In NSCLC, targeting the EGFR signalling pathway has been shown to be an effective strategy for treatment, resulting in improved clinical outcomes. The clinical success of these treatments is associated with a number of AES, including diarrhea. The efficacy of EGFR TKIS is frequently correlated with the presence of diarrhea.

The key to managing diarrhea is to educate patients about this AE before treatment starts. Patients should be monitored weekly for the first 4 weeks of treatment, which is the period during which diarrhea

TABLE III Pharmacologic intervention for diarrhea induced by epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs)²¹, based on CTCAE grade

Grade	Intervention
1 Mild	Stop laxatives. Drink 8–10 glasses of clear fluids daily. Immediately start loperamide: 4 mg (2 tablets) followed by 2 mg (1 tablet) after each loose stool (up to 20 mg daily) until bowel movements cease for 12 hours. Maintain dose level of EGFR TKI.
2 Moderate	See grade 1. Continue loperamide. Assess for dehydration and electrolyte imbalance. Consider intravenous fluids and electrolyte replacement. If diarrhea does not improve after 48 hours, temporarily discontinue EGFR TKI. Upon improvement to grade 1, restart EGFR TKI at a reduced dose (except gefitinib, which should be restarted at the original dose).
3 Severe	See grade 2 Plus: Use stool cultures to rule out an infectious process. Apply aggressive intravenous fluid replacement for 24 hours or more. Use hospitalization to monitor the patient's progress. Consider prophylactic antibiotics if the patient is also neutropenic. Temporarily discontinue EGFR TKI. Upon improvement to grade 1, restart EGFR TKI at a reduced dose (except gefitinib, which should be restarted at the original dose). Permanently discontinue EGFR TKI if diarrhea does not return to grade 1 within 14 days despite treatment discontinuation and best supportive care.
4 Life-threatening	See grade 3
5 Death	

CTCAE = *Common Terminology Criteria for Adverse Events* (version 4.03)²⁷.

will most likely occur. Nonpharmacologic management strategies include dietary changes, supplemental hydration, and electrolyte replenishment. Pharmacologic strategies include the avoidance of laxatives and the introduction of loperamide or diphenoxylate-atropine. Early management of EGFR TKI-induced diarrhea can lower the incidence of high-grade events that could lead to hospitalization and drug discontinuation and, most importantly, can improve quality of life for this group of patients.

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VH has participated on the advisory boards of Boehringer Ingelheim, Roche, AstraZeneca, Pfizer, Amgen, and Merck. NB has participated on the advisory panel of Boehringer Ingelheim. SV has received honoraria from or participated on the advisory boards of Boehringer Ingelheim, Roche, AstraZeneca, and Pfizer, and has received research funding from Roche and Sanofi. KC has participated on advisory boards for Takea National and Boehringer Ingelheim and has received educational grants from Ferring, AbbVie, and Janssen. RB has no financial conflict of interest relating to this paper.

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Correspondence to: Vera Hirsh, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec H3A 1A1.

E-mail: vera.hirsh@muhc.mcgill.ca

* Hematology-Oncology Services, Santa Cabrini Hospital, and Department of Oncology, Faculty of Medicine, McGill University, Montreal, QC.

† Department of Medicine, University of Montreal, Montreal, QC.

‡ Division of Hematology/Medical Oncology, University of Toronto, Mount Sinai Hospital, and The Princess Margaret Hospital Cancer Centre, Toronto, ON.

§ University of Toronto and Medical Oncology/Hematology, Sunnybrook Health Sciences Centre, Toronto, ON.

|| University of Toronto, and Division of Gastroenterology, Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, Toronto, ON.