# Managing treatment-related adverse events associated with EGFR tyrosine kinase inhibitors in advanced non-small-cell lung cancer

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## ABSTRACT

Non-small-cell lung cancer (NSCLC) has the highest prevalence of all types of lung cancer, which is the second most common cancer and the leading cause of cancer-related mortality in Canada. The need for more effective and less toxic treatment options for NSCLC has led to the development of agents targeting the epidermal growth factor receptor (EGFR)–mediated signalling pathway, such as EGFR tyrosine kinase inhibitors (EGFR-TKIS). Although EGFR-TKIS are less toxic than traditional anti-neoplastic agents, they are commonly associated with acneiform-like rash and diarrhea. This review summarizes the clinical presentation and causes of EGFR-TKI–induced rash and diarrhea, and presents strategies for effective assessment, monitoring, and treatment of these adverse effects. Strategies to improve the management of EGFR-TKI–related adverse events should improve clinical outcomes, compliance, and quality of life in patients with advanced NSCLC.



## KEY WORDS

Epidermal growth factor receptor, adverse drug reaction, adverse drug event, skin rash, diarrhea


## 1. INTRODUCTION

Lung cancer remains the second most common cancer and the leading cause of cancer-related mortality in Canada. In 2010, 24,400 new lung cancer cases and 20,600 related deaths were predicted, representing a significant health care burden [1]. The most common form of lung cancer, non-small-cell lung cancer (NSCLC), consists of a heterogeneous group of histologies, of which adenocarcinoma, squamous cell carcinoma, and large-cell anaplastic carcinoma are the most frequent [2]. Despite recent advances in treatment, prognosis is generally poor in patients with advanced NSCLC, and the median survival rate is only 10–12 months with treatment [3].

First-line treatment for NSCLC is usually platinum-based two-drug combination chemotherapy, with or without bevacizumab for non-squamous pathology. For patients with poor performance status, single-agent chemotherapy is often recommended, but little evidence exists to guide recommendations in this patient group [4–6]. Despite the success of platinum doublets in first-line treatment, the introduction of a third chemotherapeutic agent increases toxicity without improving efficacy [7]. The standard approach is to give a chemotherapy agent as second-line treatment or an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). The EGFR-TKIS are better tolerated, have a more convenient method of administration, and can be given for longer periods of time [7]. In addition, patients with late-stage NSCLC are often symptomatic and experience comorbidities that affect quality of life [8]. Effective treatment options of lower toxicity are therefore needed for patients with advanced NSCLC.

The need for more effective and less toxic treatment options for NSCLC has led to the development of targeted agents such as EGFR inhibitors. A number of solid tumours, including 40%–80% of NSCLC tumours, express or overexpress EGFR. Several studies showed that high EGFR expression is associated with poor prognosis in lung cancer patients. Consequently, EGFR is an attractive target for the treatment of NSCLC [8,9].

Various clinical trials have demonstrated that EGFR inhibitors are clinically efficacious in the management of several solid tumour types, such as those of breast, colon, pancreas, head and neck, kidney, gastrointestinal stroma, and lung [10]. The EGFR-TKIS impede phosphorylation of the intracellular tyrosine kinase component of EGFR and thus block signal transduction pathways associated with the proliferation and survival of cancer cells [8]. Given as second- or third-line therapy in advanced NSCLC, the EGFR-TKIS are clinically efficacious compared with supportive care or chemotherapy [8,11–14].

Erlotinib is an EGFR-TKI that has been approved in the United States, Canada, and many other countries

around the world for use in NSCLC, based on clinical trial results showing it to be safe and efficacious. Another EGFR-TKI, gefitinib, was recently granted marketing authorization by the European Medicines Agency, the United States, and Canada for the treatment of *EGFR* mutation–positive NSCLC [7]. Newer EGFR-TKIs such as afatinib (BIBW 2992) and PF-00299804 are currently in development [15–21,a].

Although targeted agents are generally less toxic than traditional anti-neoplastic agents, EGFR-TKIs are associated with a number of bothersome adverse effects that need to be managed in most patients. Because EGFR is expressed mainly on cells of epithelial origin, such as those of the skin and gastrointestinal tract, the most common adverse events of the EGFR inhibitors are rash and diarrhea, which are the focus of the present paper. Strategies to improve the assessment and management of EGFR-TKI–related adverse events such as rash and diarrhea should result in superior clinical outcomes, better compliance, and improved quality of life for patients with advanced NSCLC [10].

## 2. RASH INDUCED BY EGFR-TKIs

### 2.1 Patient Monitoring

Before initiating treatment with an EGFR-TKI, physicians should educate their patients about the associated potential side effects so that such reactions can be managed early and effectively. Because symptoms of rash generally appear as early as 2 weeks into treatment, early monitoring is essential [10].

Patients should be advised that rash is a common complication of EGFR inhibitors and an indication of treatment efficacy [22]. To prevent dose reduction or discontinuation of therapy, it is also important to inform patients that early treatment of rash can prevent symptoms from worsening.

Although not recommended in current guidelines, prophylactic treatments to prevent EGFR-TKI–induced rash have been studied in a number of trials. One randomized double-blind trial compared prophylactic oral minocycline with placebo in patients treated with cetuximab for metastatic colorectal cancer ($n$ = 48) [23]. Patients were also randomized to receive topical tazarotene applied either to the left or the right side of the face. After 4 weeks of treatment with cetuximab, the minocycline group had a significantly lower total facial lesion count ($p = 0.005$). A trend was also observed suggesting that a lower proportion of treated patients were experiencing moderate-to-severe itching (20% vs. 50% receiving placebo, $p = 0.05$). The use of topical tazarotene provided no clinical benefit and was associated with significant skin irritation.

A second randomized double-blind trial in patients ($n$ = 61) receiving EGFR-TKIs compared prophylactic tetracycline treatment (500 mg twice daily) with placebo over 4 weeks [24]. Although tetracycline did not prevent rash, a reduction in the severity of rash was observed. At week 4, grade 2 rash was reported in 17% of the tetracycline group and in 55% of the placebo group ($p = 0.04$). Treatment also improved certain quality-of-life measures, including skin burning or stinging and skin irritation.

The STEPP (Skin Toxicity Evaluation Protocol with Panitumumab) study compared primary pre-emptive skin treatment with reactive skin treatment in patients receiving panitumumab in a randomized prospective study [25]. Patients on the pre-emptive arm received daily skin treatment for a total of 6 weeks, starting 24 hours before the first dose of panitumumab. Pre-emptive treatment included skin moisturizer, sunscreen, 1% hydrocortisone cream, and doxycycline 100 mg twice daily. Patients on the reactive arm received treatment after the development of rash. Compared with reactive treatment, pre-emptive treatment reduced the incidence of grade 2 or greater rash by more than 50%, without additional side effects. Time to first occurrence of grade 2 or greater rash was also significantly delayed in the pre-emptive arm. Additional research is needed to determine the benefit of prophylactic treatment for the prevention of EGFR-TKI–induced rash.

During the first 6 weeks of treatment, patients should be assessed weekly for any signs of rash. When symptoms of rash are apparent, early intervention is of key importance to prevent more serious complications. After 6 weeks of treatment, assessment of skin toxicities can be performed less frequently—for example, every 6–8 weeks. Rash assessment can be performed by any member of the health care team who is able to reliably evaluate it.

### 2.2 Causes and Incidence

Epidermal growth factor plays an integral role in the growth and keratinization of skin epithelium, and EGFRs are expressed within the follicular epithelium, sebaceous glands, and dermal capillaries. It is therefore not surprising that EGFR inhibition leads to a number of skin reactions [10,26].

Adverse skin reactions occur in more than 50% of patients given EGFR inhibitors; they are the most common treatment-related adverse events. Skin reactions associated with EGFR inhibitors include xerosis (dry skin), pruritus, hair changes and alopecia, nail alterations, and hand and foot reactions [10,26,27]. The most common skin reaction reported in patients treated with EGFR-TKIs is a follicular acneiform eruption also known as "acne-like rash" or "folliculitis." Inhibition of EGFR is thought to alter keratinocyte proliferation, differentiation, migration, and attachment, which may explain the papulopustular reaction and xerosis seen with EGFR-TKIs[30].

Incidence of rash with EGFR-TKIs varies from 37%–78% in phase III clinical trials and appears to be

[a] See also NCT01085136, NCT01121393, NCT01000025, and NCT00769067 at clinicaltrials.gov/ct2/search.

dose-dependent (Table I). Table II presents a detailed description of the clinical trials that have examined the incidence of rash with EGFR-TKIs in NSCLC.

When rash is not adequately managed, treatment compliance may be negatively affected, leading to dose modifications or treatment discontinuation, and ultimately reducing the overall clinical benefits of treatment. Appropriate strategies are therefore needed to assess and manage EGFR-TKI–induced rash [10,45].

### 2.3 Assessment and Grading

Acneiform rash is defined as an eruption of papules and pustules, typically appearing on the face, scalp, upper chest, and back [46]. Although EGFR-TKI–induced rash most closely resembles acneiform rash in presentation, no comedones or blackheads are visible [10] (Figure 1). Rash induced by EGFR-TKI usually appears within 2 weeks of treatment start and generally presents on the face, shoulders, and upper part of the back and chest. The rash tends to improve over time with continued use of the medication and resolves fully after discontinuation of treatment [10,26]. However, in about 35% of patients, dry itchy skin of the arms and legs may occur, which can potentially become secondarily infected with a *Staphylococcus aureus* or *Herpes simplex* infection [10].

The U.S. National Cancer Institute (NCI) *Common Terminology Criteria for Adverse Events* (CTCAE) are typically used to grade symptoms for clinical trials, but those criteria have some limitations for describing EGFR-TKI–induced rash [46] (Table III). The CTCAE grading uses the affected percentage of body surface area to assess rash severity, but EGFR-TKI–induced rash is typically restricted to the face, scalp, and upper torso. The CTCAE grading also does not take into account the severity of rash complications, which may include oozing, burning, crusting, or disfigurement [47]. Given that no other standard exists for grading EGFR-TKI–induced rash, the CTCAE grading remains the standard for assessment.

TABLE I Incidence of acneiform rash with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in non-small-cell lung cancer trials

| *EGFR-TKI* | *Description* | *Grades (%)* | |
|---|---|---|---|
| | | *All* | *≥3* |
| Erlotinib 150 mg | All studies | 33–79 | 3–10 |
| | Phase III studies | 62–76 | 3–10 |
| Gefitinib 250 mg and 500 mg | All studies | 34–75 | 0–13 |
| | 250 mg | 34–66 | 0–4 |
| | 500 mg | 57–75 | 4–13 |
| | Phase III studies | 37–67 | 2–13 |
| | 250 mg | 37–66 | 2–4 |
| | 500 mg | 57–67 | 12–13 |
| Afatinib 40 mg and 50 mg | All studies | 67–100 | 0–25 |
| | 40 mg | 90–100 | 0–7 |
| | 50 mg | 67–92 | 0–25 |
| | Phase III studies | 78 | 14 |
| | 50 mg | | |
| PF-00299804 30 mg and 45 mg | All studies (phase II)[a] | 68–100 | 0–15 |
| | 30 mg | 69 | 0 |
| | 45 mg | 68–85 | 15 |

[a] No phase III study results using PF-00299804 are available to date.

### 2.4 Management

Before initiating EGFR-TKI therapy, physicians should counsel their patients about preventive measures to reduce the risk of skin rash. The educational messages that need to be communicated to patients being prescribed EGFR-TKIs are these[10,22,27,45]:

- Any areas of dry skin should be moisturized twice daily using a thick, alcohol-free emollient.
- Sun exposure should be minimized. Where sun exposure is unavoidable, a broad-spectrum sunscreen with a sun protection factor of 15 or higher should be applied 1–2 hours before exposure, especially on the face and upper body. Physical sunscreens that contain zinc oxide or titanium dioxide are preferable to chemical sunscreens.
- Products that dry the skin—such as soaps, alcohol-based or perfumed products, and over-the-counter acne products—should be avoided. Because long hot showers can also dry the skin, shower time should be limited, and lukewarm water should be used.

A number of treatment algorithms have been proposed for the management of skin rash induced by EGFR inhibitors; the algorithm presented in Figure 2 represents an amalgam of existing frameworks [10,27,48–50].

The EGFR-TKI dosage should remain unchanged for all patients, except those with severe rash (grade 3 or higher). Patients with mild toxicities (grade 1) may need no intervention; however, treatment with topical hydrocortisone (1% or 2.5% cream) or clindamycin (1% gel) is reasonable. For patients with moderate toxicities (grade 2), treatment with hydrocortisone (2.5% cream), clindamycin (1% gel), or pimecrolimus (1% cream) is recommended, with the addition of either oral doxycycline (100 mg twice daily) or minocycline (100 mg twice daily). For patients with severe toxicities (grade 3 or higher), concomitant intervention is the same as for moderate toxicities, with the addition of a methylprednisolone dose pack (a package containing a specific number of pills to be taken at designated times over a period of a few days). If the rash does not dissipate sufficiently within 2–4 weeks, interruption of EGFR inhibitor therapy is

TABLE II Incidence of rash and diarrhea with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in non-small-cell lung cancer (NSCLC) clinical trials

| *EGFR-TKI* | *Reference (study name)* | *Description* | *Patients (n)* | *Grades of rash (%)* | | *Grades of diarrhea (%)* | |
|---|---|---|---|---|---|---|---|
| | | | | *All* | *≥3* | *All* | *≥3* |
| Erlotinib | All studies | Dose: 150 mg | | 33–79 | 3–10 | 10–69 | 0–17 |
| | Herbst *et al.,* 2005 [28] (TRIBUTE) | Phase III; erlotinib 150 mg vs. placebo; first-line combination therapy with paclitaxel and carboplatin; chemotherapy-naïve | Total: 1079<br>Erlotinib: 539<br>Placebo: 540 | 61.7 | 7.2 | 67.9 | 12.4 |
| | Shepherd *et al.,* 2005 [11] (BR.21) | Phase III; erlotinib 150 mg vs. placebo; second- or third-line monotherapy after failure with standard first- or second-line chemotherapy | Total: 731<br>Erlotinib: 488<br>Placebo: 243 | 76 | 9 | 55 | 6 |
| | Cho *et al.,* 2007 [29] | Phase II; second-line erlotinib 150 mg after failure with gefitinib | Total: 21 | 33.3 | 4.8 | 9.5 | 0 |
| | Gatzemeier *et al.,* 2007 [30] (TALENT) | Phase III; erlotinib 150 mg vs. placebo; first-line combination therapy with gemcitabine and cisplatin; chemotherapy-naïve | Total: 1172<br>Erlotinib: 586<br>Placebo: 586 | NR | 10 | 40 | 6 |
| | Jackman *et al.,* 2007 [31] | Phase II; first-line erlotinib 150 mg; chemotherapy-naïve | Total: 80 | 78.8 | 6 | 68.8 | 5 |
| | Felip *et al.,* 2008 [12] | Phase II; second-line erlotinib 150 mg after failure with platinum-based chemotherapy | Total: 83 | 61 | 7 | 23 | 2 |
| | Lilenbaum *et al.,* 2008 [32] | Phase II; first-line erlotinib 150 mg vs. chemotherapy (carboplatin and paclitaxel); chemotherapy-naïve | Total: 103<br>Erlotinib: 52<br>Chemotherapy: 51 | 65 | 8 | 44 | 6 |
| | Mok *et al.,* 2009 [33] (FAST-ACT) | Phase II; first-line sequential erlotinib 150 mg and platinum-based doublet chemotherapy [gemcitabine and cisplatin (GC) or carboplatin] vs. chemotherapy alone | Total: 154<br>GC+erlotinib: 76<br>GC+placebo: 78 | 65 | 3 | 22 | 0 |
| | Bennouna *et al.,* 2010 [34] | Phase II; everolimus plus erlotinib 150 mg (EE) vs. erlotinib 150 mg monotherapy (EM); previously-treated patients | Total: 133<br>EE: 66<br>EM: 67 | NR | NR | NR | EE: 8<br>EM: 5 |
| | Groen *et al.,* 2010 [35] | Phase II; sunitinib plus erlotinib 150 mg (SE) vs. placebo plus erlotinib 150 mg (PE); 2 or fewer previous chemotherapy regimens, including 1 or more platinum-based regimens | Total: 132 | NR | NR | NR | SE: 17.2<br>PE: 1.6 |
| | Kelly *et al.,* 2010 [36] | Phase IIB; pralatrexate vs. erlotinib 150 mg; previously treated with platinum-based chemotherapy | Total: 201 | NR | Erlotinib: ≤10 | NR | NR |

TABLE II *Continued*

| *EGFR-TKI* | *Reference (study name)* | *Description* | *Patients (n)* | *Grades of rash (%)* | | *Grades of diarrhea (%)* | |
|---|---|---|---|---|---|---|---|
| | | | | *All* | *≥3* | *All* | *≥3* |
| | Scagliotti *et al.,* 2010 [37] | Phase III; sunitinib plus erlotinib 150 mg (SE) vs. placebo plus erlotinib 150 mg (PE); 2 or fewer previous chemotherapy regimens | Total: 960 | NR | SE: 8.2<br>PE: 2.5 | NR | SE: 10.4<br>PE: 1.7 |
| | Zhao *et al.,* 2010 [38] (ML 22206) | Phase II; erlotinib 150 mg plus capecitabine; first-line in elderly patients with advanced disease | Total: 62 | NR | NR | NR | NR |
| Gefitinib | All studies | Doses: 250 mg and 500 mg | | 34–75 | 0–13 | 27–75 | 0–25 |
| | Fukuoka *et al.,* 2003 [8] (IDEAL 1) | Phase II; second-line gefitinib 250 mg or 500 mg after failure with 1 or 2 chemotherapy regimens, at least 1 platinum-based | Total: 210<br>250-mg Arm: 104<br>500-mg Arm: 106 | 250 mg: 46.6;<br>500 mg: 68.9 | 250 mg: 1;<br>500 mg: 6.6 | 250 mg: 39.8;<br>500 mg: 57.5 | 250 mg: 0;<br>500 mg: 6.6 |
| | Kris *et al.,* 2003 [39] (IDEAL 2) | Phase II; gefitinib 250 mg vs. gefitinib 500 mg after failure with 2 or more chemotherapy regimens containing cisplatin or carboplatin and docetaxel | Total: 221<br>Gefitinib 250 mg: 106<br>Gefitinib 500 mg: 115 | 250 mg: 62;<br>500 mg: 75 | 250 mg: 0;<br>500 mg: 4 | 250 mg: 57;<br>500 mg: 75 | 250 mg: 1;<br>500 mg: 5 |
| | Giaccone *et al.,* 2004 [40] (INTACT 1) | Phase III; gefitinib 250 mg or 500 mg vs. placebo; first-line combination therapy with gemcitabine and cisplatin; chemotherapy-naïve | Total: 1093<br>Gefitinib 250 mg: 365<br>Gefitinib 500 mg: 365<br>Placebo: 363 | 250 mg: 44.5;<br>500 mg: 56.7 | 250 mg: 3.6;<br>500 mg: 12.6 | 250 mg: 28.7;<br>500 mg: 50.8 | 250 mg: 3.6;<br>500 mg: 12.0 |
| | Herbst *et al.,* 2004 [41] (INTACT 2) | Phase III; gefitinib 250 mg or 500 mg vs. placebo; first-line combination therapy with paclitaxel and carboplatin; chemotherapy-naïve | Total: 1037<br>Gefitinib 250 mg: 345<br>Gefitinib 500 mg: 347<br>Placebo: 345 | 250 mg: 54.4;<br>500 mg: 67.3 | 250 mg: 3.2;<br>500 mg: 11.7 | 250 mg: 58.2;<br>500 mg: 69.3 | 250 mg: 9.9;<br>500 mg: 25.4 |
| | Thatcher *et al.,* 2005 [13] (ISEL) | Phase III; second- or third-line gefitinib 250 mg vs. placebo after failure of 1 or 2 previous chemotherapy regimens | Total: 1692<br>Gefitinib: 1129<br>Placebo: 563 | 37 | 2 | 27 | 3 |
| | Kim *et al.,* 2008 [14] (INTEREST) | Phase III; second-line gefitinib 250 mg vs. docetaxel after failure with up to 2 chemotherapy regimens, at least 1 platinum-based | Total: 1466<br>Gefitinib: 733<br>Docetaxel: 733 | 49.4 | 2.1 | 35.0 | 2.5 |
| | Goss *et al.,* 2009 [42] (INSTEP) | Phase II; first-line gefitinib 250 mg vs. placebo; chemotherapy-naïve | Total: 201<br>Gefitinib: 100<br>Placebo: 101 | 34 | 0 | 51 | 3 |

TABLE II *Continued*

| *EGFR-TKI* | *Reference (study name)* | *Description* | *Patients (n)* | *Grades of rash (%)* | | *Grades of diarrhea (%)* | |
|---|---|---|---|---|---|---|---|
| | | | | *All* | *≥3* | *All* | *≥3* |
| | Mok *et al.,* 2009 [43] (IPASS) | Phase III; first-line gefitinib 250 mg vs. carboplatin plus paclitaxel (CP); chemotherapy-naïve | Total: 1217<br>Gefitinib: 609<br>CP: 608 | 66.2 | 3.1 | 46.6 | 3.8 |
| | Surmont *et al.,* 2010 [44] (EORTC 08021–ILCP) | Phase III; maintenance gefitinib 250 mg vs. placebo; patients non-progressing on 4 cycles of platinum-based chemotherapy | Total: 173<br>Gefitinib: 86<br>Placebo: 87 | 40<br>- | NR | 29 | NR |
| Afatinib (BIBW 2992) | All studies | Doses: 20 mg, 40 mg, 50 mg | | 33–100 | 0–25 | 0–100 | 0–33 |
| | Miller *et al.,* 2010 [15] (LUX-Lung 1) | Phase IIB/III; afatinib 50 mg vs. placebo after failure with chemotherapy (including platinum) and erlotinib or gefitinib | Total: 585<br>Afatinib: 390<br>Placebo: 195 | 78 | 14 | 87 | 17 |
| | Yamamoto *et al.,* 2010 [17] (LUX-Lung 4) | Phase I; afatinib 20 mg, 40 mg, or 50 mg after failure with any combination of chemotherapy, erlotinib, and gefitinib | Total: 12 | 20 mg: 33.3<br>40 mg: 100<br>50 mg: 66.7 | 20 mg: 0<br>40 mg: 0<br>50 mg: 0 | 20 mg: 0<br>40 mg: 66.7<br>50 mg: 100 | 20 mg: 0<br>40 mg: 0<br>50 mg: 33.3 |
| | Yang *et al.,* 2010 [16] (LUX-Lung 2) | Phase II; afatinib 40 mg or 50 mg in patients with activating *EGFR* mutations after failure with 1 chemotherapy regimen and no previous EGFR-TKI | Total: 129 | 40 mg: 90.0<br>50 mg: 91.9 | 40 mg: 6.7<br>50 mg: 25.3 | 40 mg: 96.7<br>50 mg: 93.9 | 40 mg: 6.7<br>50 mg: 21.2 |
| | Ongoing study [18] (LUX-Lung 5) | Phase III; afatinib 40 mg plus paclitaxel vs. investigator's choice of single-agent chemotherapy after progression with afatinib monotherapy | Total: 900 | NR | NR | NR | NR |
| | Ongoing study [19] (LUX-Lung 6) | Phase III; afatinib vs. cisplatin plus gemcitabine; first-line in patients with *EGFR* activating mutation | Total: 330 | NR | NR | NR | NR |
| PF-00299804 | All studies | Doses: 15 mg, 30 mg, and 45 mg | | 68–100 | 0–15 | 77–97 | 0–15 |
| | Janne *et al.,* 2009 [20] (A7471002) | Phase II; PF-00299804 45 mg in adenocarcinoma and non-adenocarcinoma patients after failure with at least 1 chemotherapy regimen and erlotinib | Total: 34<br>Adenocarcinoma: 30<br>Non-adenocarcinoma: 4 | 84.9 | 15.1 | 81.1 | 13.2 |
| | Mok *et al.,* 2010 [20] | Phase II; first-line PF-00299804 30 mg or 45 mg in advanced NSCLC with *EGFR* mutation | Total: 74 | 30 mg: 69<br>45 mg: 68 | 30 mg: 0<br>45 mg: 15 | 30 mg: 77<br>45 mg: 97 | 30 mg: 0<br>45 mg: 15 |

TABLE II *Continued*

| *EGFR-TKI* | *Reference (study name)* | *Description* | *Patients (n)* | *Grades of rash (%)* | | *Grades of diarrhea (%)* | |
|---|---|---|---|---|---|---|---|
| | | | | *All* | *≥3* | *All* | *≥3* |
| | Ramalingam *et al.*, 2010[19] | Phase II; PF-00299804 45 mg vs. erlotinib 150 mg in advanced NSCLC patients who were erlotinib-naïve and had failed at least 1 chemotherapy regimen | Total: 188<br>Erlotinib: 94<br>PF-00299804: 94 | Tolerable in both agents | | Tolerable in both agents | |
| | Takahashi *et al.*, 2010[21] | Phase I; PF-00299804 15 mg, 30 mg, or 45 mg in advanced solid-tumour patients who had failed all standards of care | Total: 13 | 100[a] | 45 mg: 15.4 | 92[a] | NR |
| | Ongoing study[24] (BR.26) | Phase III; PF-00299804 45 mg vs. placebo in advanced NSCLC patients after failure with at least 1 chemotherapy regimen and erlotinib or gefitinib (or both) | Total: 720 | NR | NR | NR | NR |
| | Ongoing study[25] (A7471028) | Phase II; PF-00299804 45 mg vs. erlotinib 150 mg in advanced NSCLC patients after failure with at least 1 chemotherapy regimen | Total: 160 | NR | NR | NR | NR |

[a] Adverse events by dose subgroup not given.
NR = not reported; EORTC = European Organisation for Research and Treatment of Cancer.



*FIGURE 1* *Rash induced by epidermal growth factor receptor.*

TABLE III U.S. National Cancer Institute grading for acneiform rash[a]

| | |
|---|---|
| Grade 1 | Papules or pustules, or both, covering less than 10% of body surface area, which may or may not be associated with symptoms of pruritus or tenderness |
| Grade 2 | Papules or pustules, or both, covering 10%–30% body surface area, which may or may not be associated with symptoms of pruritus or tenderness<br>Associated with psychosocial impact<br>Limits instrumental activities of daily living |
| Grade 3 | Papules or pustules, or both, covering more than 30% body surface area, which may or may not be associated with symptoms of pruritus or tenderness<br>Limits self-care activities of daily living<br>Associated with local superinfection, with oral antibiotics indicated |
| Grade 4 | Papules or pustules, or both, covering any percentage of body surface area, which may or may not be associated with symptoms of pruritus or tenderness and which are associated with extensive superinfection, with intravenous antibiotics indicated<br>Life-threatening consequences |
| Grade 5 | Death |

[a] Adapted from the *Common Terminology Criteria for Adverse Events,* 2010[46].

recommended in accordance with the prescribing information[10,27].

Novel treatments for EGFR-TKI–induced rash, such as menadione lotion, retinoids, and alpha-hydroxy acids, are under investigation in preliminary studies. However, until controlled studies are performed, their efficacy remains unknown, because rash often resolves spontaneously in patients taking EGFR-TKIS[47].

Because the half-life of EGFR-TKIS is long, management of adverse skin reactions should continue

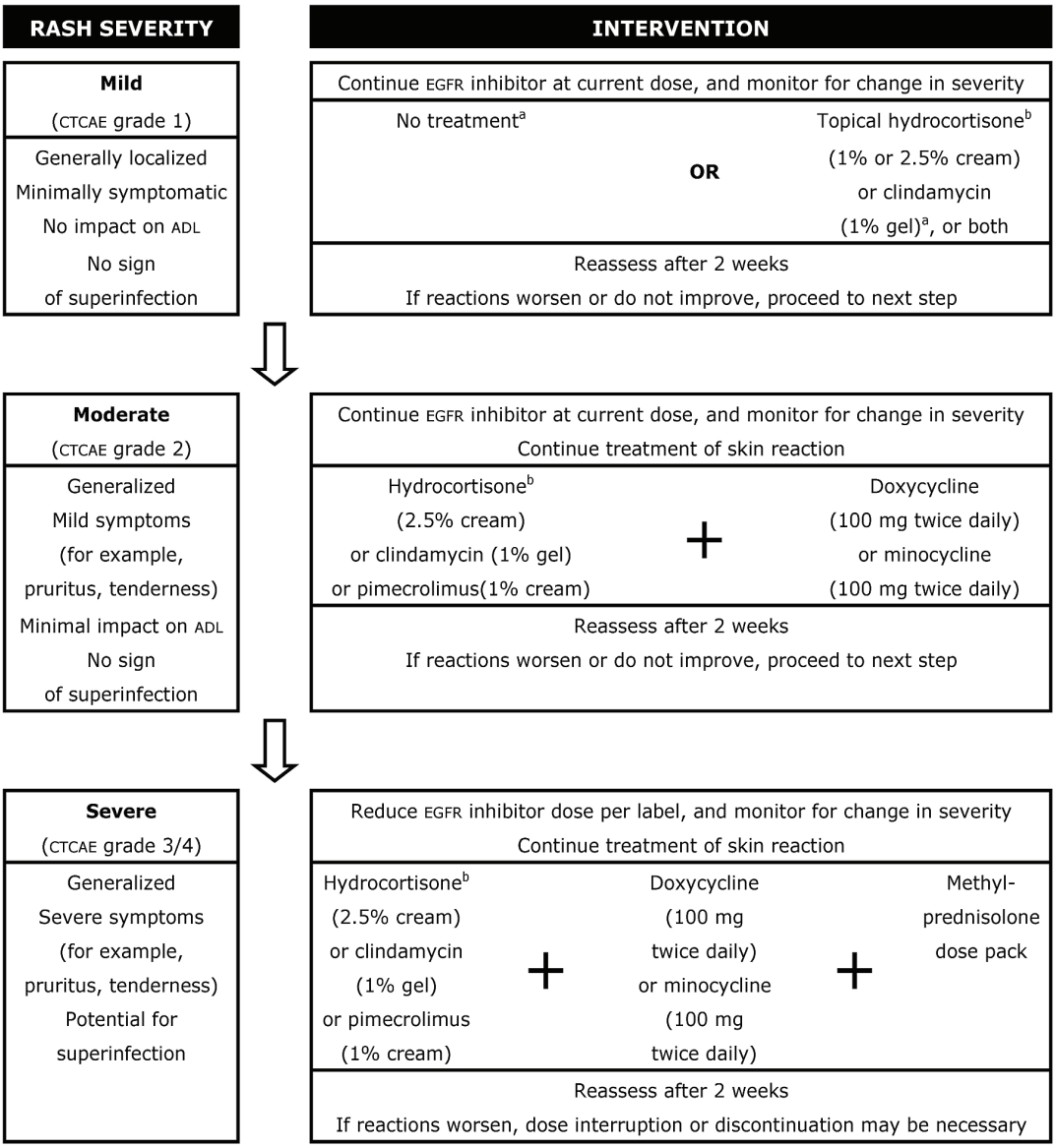


*FIGURE 2* *Management of rash induced by epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI).* CTCAE = Common Terminology Criteria for Adverse Events; ADL = *activities of daily living. Adapted from Eaby* et al., *2008* [48]; *Harandi* et al., *2009* [27]; *Lynch* et al., *2007* [10].

[a] *Guidelines presented here recommend treatment with minocycline for moderate-to-severe rash only. However, early treatment of mild rash can prevent the development of more severe forms and the need for higher, more toxic doses of minocycline. Early treatment of mild rash with 50 mg minocycline plus 1% hydrocortisone is therefore a reasonable option.*

[b] *Topical steroids should be pulsed according to institution guidelines.*

until those reactions have sufficiently diminished or resolved, even if treatment is discontinued or reduced. Once adverse reactions have sufficiently resolved, EGFR-TKI therapy may be restarted or escalated to the original dosing scheme, with reasonable confidence that toxicities will be well managed [27].

### 2.5 Rash As an Indicator of Treatment Response

Numerous studies have shown a significant correlation between skin rash severity and response to EGFR inhibitor treatment [10,26,47]. In NSCLC, several gefitinib and erlotinib trials have supported that finding [22,39,51].

A phase II study by Kris *et al.* [39] (IDEAL) examined the efficacy and safety of gefitinib (250 mg vs. 500 mg daily) in patients with pre-treated advanced NSCLC. Although efficacy outcomes were similar across dose groups, skin toxicity was reported in 86% of patients (72 of 84) with symptom improvement [a 2-point increase in score on the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale], but in only 58% of patients (76 of 132) with

no symptom improvement (observed difference: 28%; 95% confidence interval: 17% to 39%). A retrospective study by Mohamed *et al.* [51] analyzed the clinical characteristics of patients who were associated with survival after treatment with gefitinib as part of the Expanded Access Program. Median survival was longer in patients who developed skin rash than in those who did not (10.8 months vs. 4.0 months, $p < 0.0001$) [26,51].

A phase III study by Shepherd *et al.* [11] (BR.21) examined the efficacy and safety of erlotinib in patients with pre-treated advanced NSCLC. Rash occurred in 76% of patients given erlotinib (368 of 485), with 9% experiencing severe (grade 3 or higher) rash. A retrospective study by Wacker *et al.* [22] analyzed the association between rash and clinical outcome using data from the study by Shepherd and colleagues and also data from a phase III study comparing single-agent gemcitabine with gemcitabine plus erlotinib as first-line therapy for advanced pancreatic cancer (PA.3) [52]. The response rate was 1% among patients who did not develop rash compared with 10% among those who developed grade 1 rash and 13% among those who developed grade 2 or higher rash (grade 1 vs. grade 0, $p = 0.048$; grade 2 vs. grade 0, $p = 0.017$). After controlling for baseline factors in multivariate analyses, the presence of rash correlated strongly with overall and progression-free survival; the correlations increased with rash severity ($p < 0.05$) [22,26].

The positive relationship between skin rash and response or survival (or both) suggests that rash could be a potential surrogate marker for EGFR-TKI efficacy. Whether rash reflects the local effects of EGFR inhibition in skin or indicates a systemic inflammatory reaction, it may serve as a useful pharmacodynamic marker of target inhibition [22]. The relationship between rash and survival is currently being evaluated in ongoing studies, and results should help guide the use of EGFR-TKIS.

## 3. DIARRHEA INDUCED BY EGFR-TKIs

### 3.1 Patient Monitoring and Diarrhea Causes and Incidence

Patients should be advised to immediately discuss any symptoms of diarrhea with their health care team. The diarrhea can then be managed early and effectively, preventing dose reductions or treatment discontinuation.

Because diarrhea is a common side effect of many cancer treatment regimens, management of diarrhea in the oncology setting is well established [53–55]. Diarrhea induced by EGFR-TKIS is thought to be a result of excess chloride secretion, causing a secretory form of diarrhea [10]. Severe diarrhea can result in fluid and electrolyte losses, which may lead to dehydration, electrolyte imbalances, and renal insufficiency. Nutritional deficiencies can also develop from alterations in gastrointestinal transit and digestion, negatively affecting a patient's quality of life [55].

The incidence of diarrhea with EGFR-TKIS varies from 27% to 87% in phase III clinical trials, with up to 25% of patients experiencing severe reactions (grade 3 or higher; Table IV). Table II gives a detailed description of the clinical trials that have examined the incidence of diarrhea with EGFR-TKIS in NSCLC.

### 3.2 Assessment and Grading

The first step in the assessment of EGFR-TKI–induced diarrhea is to rule out other potential causes. Possible causes of diarrhea include medications such as laxatives, stool softeners, antacids, or antibiotics; dietary factors, such as excess consumption of fibre or lactose; comorbid infections; intestinal obstruction; fecal impaction; surgeries such as short-bowel or gastrectomy; and radiation toxicity.

Laboratory investigations are also useful to rule out other causes of diarrhea. Recommended

TABLE IV Incidence of diarrhea with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIS) in non-small-cell lung cancer trials

| *EGFR-TKI* | *Description* | *Grade (%)* | |
|---|---|---|---|
| | | *All* | *≥3* |
| Erlotinib | All studies | 10–69 | 0–17 |
| 150 mg | Phase III studies | 40–68 | 2–12 |
| Gefitinib | All studies | 27–75 | 0–25 |
| 250 mg and 500 mg | 250 mg | 27–58 | 0–10 |
| | 500 mg | 51–75 | 5–25 |
| | Phase III studies | 27–69 | 3–25 |
| | 250 mg | 27–58 | 3–10 |
| | 500 mg | 51–69 | 12–25 |
| Afatinib | All studies | 67–100 | 0–33 |
| 40 mg and 50 mg | 40 mg | 67–97 | 0–7 |
| | 50 mg | 87–100 | 17–33 |
| | Phase III studies | | |
| | 50 mg | 87 | 17 |
| PF-00299804 | All studies (phase II)[a] | 77–97 | 0–15 |
| 15 mg, 30 mg, and 45 mg | 30 mg | 77 | 0 |
| | 45 mg | 81–97 | 13–15 |

[a] No phase III study results using PF-00299804 are available to date.

laboratory investigations include a complete blood count and differential to rule out neutropenia, blood tests to assess renal function and to determine the presence of electrolyte abnormalities, and stool culture or a *Clostridium difficile* toxin screen to identify whether bacterial pathogens are present. Other investigations may include abdominal radiography, endoscopy, or biopsy to rule out co-existing disorders such as bowel obstruction or perforation. Additional information—such as the duration of the episode, stool characteristics, and co-existing symptoms—should also be obtained during the patient evaluation [54,55].

The NCI CTCAE are generally used to grade diarrhea severity (Table V). However, because the NCI criteria do not provide a complete assessment, the additional information already described should be obtained during the patient evaluation [54,55].

### 3.3 Management

Although EGFR-TKI–induced diarrhea is usually mild to moderate, early management is essential to prevent dose reduction or discontinuation of anticancer therapies. The management of EGFR-TKI–induced diarrhea is identical to that of chemotherapy-induced diarrhea and can generally be handled using dietary changes and antidiarrheal medications [53–55].

Dietary modifications are not recommended in anticipation of diarrhea, and patients without symptoms may eat an unrestricted diet. Patients experiencing diarrhea should avoid foods that exacerbate symptoms, such as greasy, spicy, and fried items. An initial "BRAT" diet of bananas, rice, apple sauce, and toast is often helpful until symptoms begin to resolve. Foods that are difficult to digest—such as cabbage, Brussels sprouts, and broccoli—should be avoided, because those foods may increase abdominal cramping and bloating. Once diarrhea begins to improve, other foods such as pasta, chicken without skin, and eggs may be added as tolerated [53–55].

Daily fluid intake of approximately 3–4 L is recommended to avoid dehydration from volume loss attributable to diarrhea. At least some of the fluids should contain sugar or salt to avoid hyponatremia and hypokalemia caused by electrolyte loss. Good options include non-caffeinated beverages, gelatine products, and clear broths. Milk products should be avoided for about a week after a diarrhea episode because lactase activity may be diminished during prolonged diarrhea, resulting in temporary lactose intolerance [53–55].

The pharmacologic management of diarrhea is usually limited to treatment with over-the-counter loperamide (Figure 3). Patients should begin taking loperamide at the first sign of diarrhea, starting with 4 mg (2 tablets), followed by 2 mg (1 tablet) every 4 hours or after each loose stool to a maximum dose of 20 mg (10 tablets) daily. If diarrhea persists for more than 24 hours, the dose of loperamide may be increased to 4 mg, followed by 2 mg every 2 hours. After 12 hours have passed with no episodes of diarrhea, pharmacologic treatment can be stopped, and the patient's diet can be expanded as tolerated [53–56].

If patients present with grade 3 or 4 diarrhea, dose reduction or discontinuation of EGFR-TKIs may be necessary. If diarrhea fails to resolve after dose reduction or discontinuation, use of octreotide may be considered. It is very unlikely that octreotide would be needed to combat EGFR-TKI–induced diarrhea as it is for chemotherapy-induced diarrhea; no evidence supports its use in the EGFR-TKI setting. In general, most physicians would therefore discontinue EGFR-TKI therapy rather than start treatment with octreotide. Once severe diarrhea has subsided, EGFR-TKIs may be restarted at a lower dose.

TABLE V U.S. National Cancer Institute grading for diarrhea[a]

| | |
|---|---|
| Grade 1 | Increase of fewer than 4 stools per day over baseline |
| Grade 2 | Increase of 4–6 stools per day over baseline |
| Grade 3 | Increase of 7 or more stools per day over baseline |
| | Incontinence |
| | Hospitalization indicated |
| | Limits self-care activities of daily living |
| Grade 4 | Life-threatening consequences |
| | Urgent intervention indicated |
| Grade 5 | Death |

[a] Adapted from the *Common Terminology Criteria for Adverse Events,* v4.03, 2010 [46].

## 4. SUMMARY

Despite the success of platinum doublets, the need for more effective agents in the treatment of advanced NSCLC remains. Because NSCLC patients are often symptomatic and may have a number of comorbidities, effective, low-toxicity treatment options are also required. The advent of targeted therapies has led to the development of a number of less toxic anticancer agents [8,10].

Targeting the EGFR pathway has proved to be an effective strategy in a number of cancers, including NSCLC. Clinical trials using EGFR-TKIs in NSCLC have demonstrated promising anticancer activity, resulting in improved tumour control and patient survival [8,10].

Although EGFR-TKIs have been successful in improving clinical outcomes, they often result in a number of bothersome side effects, such as rash and diarrhea. Strategies to manage those adverse effects are essential to increase patient compliance,

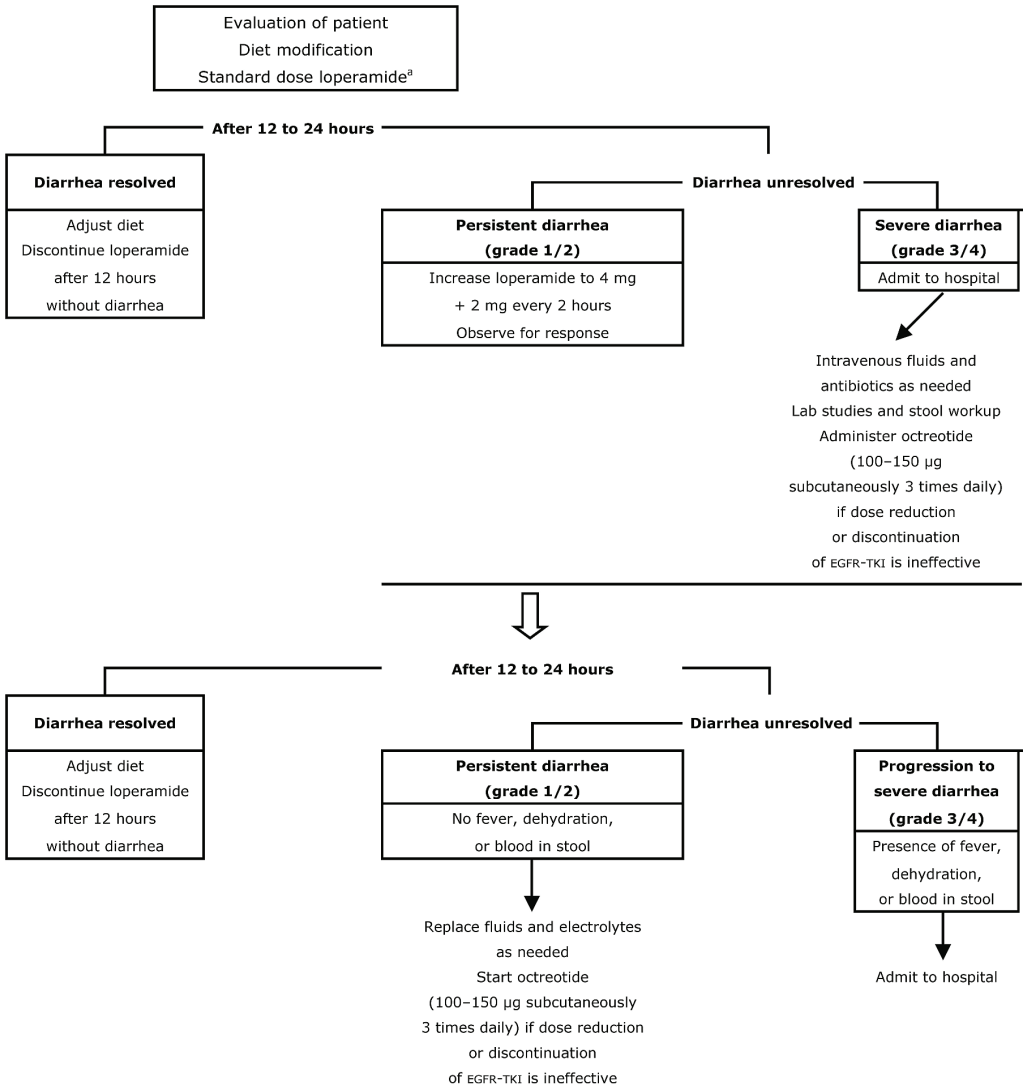


*FIGURE 3 Management of diarrhea induced by epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Adapted from BC Cancer Agency, 2004* [54]*; Moore* et al.*, 2007* [52]*; and Saltz, 2003* [53]*. [a] Starting dose is 4 mg, followed by 2 mg for a maximum of 20 mg daily.*

quality of life, and overall treatment outcome. With proper and early management, EGFR-TKIs may provide a less toxic treatment option for patients with advanced NSCLC [8,10].

## 5. CONFLICT OF INTEREST DISCLOSURES

The author acknowledges medical writing support from Anna Christofides MSC RD of SAGE Medica; her support was funded by Boehringer Ingelheim Canada.

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