

CONTINUING EDUCATION

EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Describe the mechanism of action of two epidermal growth factor receptor (EGFR) inhibitors used in the treatment of non-small cell lung cancer
- Describe the characteristics of the rash associated with EGFR inhibitors
- Identify three appropriate strategies to prevent or treat EGFR-associated rash

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Cetuximab, an EGFR inhibitor, is FDA approved for head, neck, and colon cancer but not yet approved for lung cancer. It is discussed in the article because its FDA approval for use in non-small cell lung cancer is pending.

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Managing EGFR inhibitor side effects in lung cancer patients

Beth Eaby-Sandy, CRNP, OCN

STATEMENT OF NEED/PROGRAM OVERVIEW

Treatment of lung cancer has shown promising improvements in the past 5 years. The class of drugs known as *epidermal growth factor receptor (EGFR) inhibitors* has increased response rates and overall survival. This class of drugs exhibits a common set of side effects, which nurses are often called upon to recognize and manage. The future of lung cancer treatment will include the use of EGFR inhibitors, and nurses must be equipped with the knowledge to understand the drugs, their possible toxicities, and how to properly manage the side effects.

CE INFORMATION

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Target audience: This activity has been designed to meet the educational needs of registered nurses and nurse practitioners involved in the management of patients with cancer.

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Managing EGFR inhibitor side effects in lung cancer patients

Epidermal growth factor receptor inhibitors are a mainstay of lung cancer treatment. Oncology nurses can do much to ensure their most effective use.



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Lung cancer is the leading cause of cancer deaths in the United States, resulting in more deaths per year than breast, colon, prostate, and pancreatic cancers combined.¹ In the past 5 to 10 years, significant advances in treatment have emerged, which have improved overall survival as well as response rates for metastatic non-small cell lung cancer (NSCLC). Targeted therapies have been a large part of the advances—in particular, one class of drugs called *epidermal growth factor receptor (EGFR) inhibitors*. These drugs target receptors either on the outside of cancer cells or at an intracellular domain to inhibit cell survival, metastases, angiogenesis, and inhibition of apoptosis.

EGFR INHIBITORS USED TO TREAT LUNG CANCER

Erlotinib (Tarceva) is an EGFR-tyrosine kinase inhibitor (TKI), meaning that it inhibits EGFR by gaining entrance into the cell and blocking the downstream signaling at the tyrosine kinase domain. Erlotinib is a small molecule. Drugs of this type have a different structure and work at different places in the cell than large molecule drugs; they are typically able to diffuse into cells and can act on targets that are found inside the cell. Erlotinib is orally available, which can aid or cause challenges in adherence. It is

FIGURE 1. Grade 3 rash on the chest of a patient taking erlotinib

given once daily at a recommended dose of 150 mg. Based on the results of a large, randomized, phase III clinical trial showing improved response rates and overall survival in patients taking erlotinib versus placebo, erlotinib was FDA approved for second- or third-line treatment of locally advanced or metastatic NSCLC after failure of a prior chemotherapy regimen.² The most common side effects experienced by patients in the study were rash and diarrhea. Grade 3/4 rash occurred in 9% of patients, and grade 3/4 diarrhea developed in 6% of patients.²

Cetuximab (Erbix) is another EGFR inhibitor. It is not yet FDA approved for NSCLC, but it does have a Medicare compendia approval and clinical trial data to support its use in metastatic NSCLC. Cetuximab is a monoclonal antibody that attaches to the EGFR receptor on the cell surface (large molecule), thus preventing binding of the EGF ligand to the receptor. It is available as an intravenous drug. It gained Medicare approval for use as a result of a large, randomized, phase III clinical trial commonly known as the *FLEX trial*.³ This predominantly European trial randomized chemotherapy-naïve patients with stage IIIB/IV lung cancer to receive first-line cisplatin and vinorelbine (CV) or CV plus cetuximab. Patients in the cetuximab arm showed a 2-month improvement in overall survival. The major side effects of cetuximab, as for other EGFR inhibitors, were rash and diarrhea, with grade 3/4 rash affecting 10% of patients and grade 3/4 diarrhea affecting 5% of patients.³ Cetuximab is currently awaiting FDA approval for stage IIIB/IV NSCLC.

Gefitinib (Iressa) was the first EGFR inhibitor to become available in the United States. The FDA approved it based on phase II data showing promising response rates; however, in 2005, the labeling was revised as a result of failure of the phase III trial data to show a benefit over placebo.⁴ Gefitinib is an oral tablet dosed at 250 mg daily and is a small molecule TKI. Under current labeling, it is available only to patients who were taking the drug before its use was restricted who have proven continued radiographic response to the drug.

THE TOXICITIES

The most commonly seen toxicity from EGFR inhibitors is a papulopustular rash that erupts most often on the face but can also be seen on the chest, back, trunk, and limbs (**Figure 1**). It tends to be associated with dry skin and at times can be diffuse and very disruptive to activities of daily living. The rash commonly manifests in the first 1 to 2 weeks of treatment. **Table 1** provides information on incidence and severity. Other skin and hair side effects of EGFR inhibitors are mild to moderate alopecia,

paronychias, conjunctivitis, hypertrichosis, skin fissures, and generalized pruritus.

Diarrhea is another common class effect of these drugs. It can be seen at any time during treatment with EGFR inhibitors. Severe diarrhea occurred in about 3% to 6% of the patients taking erlotinib, cetuximab, or gefitinib in phase III trials. Other less common GI side effects can be nausea and vomiting, anorexia, and stomatitis.

Infusion reactions have been seen with cetuximab, which is a monoclonal antibody with some murine properties. The rate of grade 3/4 infusion reactions with cetuximab was about 4% in the lung cancer trial.³ Some electrolyte imbalances, such as hypomagnesemia and hypokalemia, have been more common in patients taking cetuximab and are often exacerbated by diarrhea. The rates of grade 3/4 hematologic side effects were generally similar in patients receiving chemotherapy alone and those also receiving cetuximab,³ and hematologic side effects are generally not significant with EGFR inhibitors. Febrile neutropenia was more significant in the cetuximab-containing arm of the *FLEX trial* (cetuximab, 22%; chemotherapy only, 15%; $P = .0086$), although the grade 3/4 neutropenia rates were exactly the same.³

In the EGFR-TKIs, rare but statistically significant occurrences of interstitial lung disease (ILD) have been reported. This disease manifests as acute-onset dyspnea, usually occurring over a 24- to 48-hour period. ILD is an acute inflammation of lung tissue as a reaction to the drug and is a reason for permanent discontinuation of therapy. CT of the chest is often diagnostic and shows an inflammatory process within the lungs. In studies of gefitinib, ILD occurred in 0.3% to 1% of the US population and in about 2% of Japanese patients.⁵ ILD rates in the BR.21 erlotinib trial were less than 1%.²

STRATEGIES FOR MANAGING EGFR INHIBITOR-INDUCED RASH

The treatment of EGFR inhibitor-induced rash starts with a method to identify and grade the rash. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) scale is the most commonly used way to grade cancer treatment toxicities. The current version 4.0 lists different skin rashes and skin conditions that can occur

TABLE 1. Rash reported in phase III lung cancer trials

	Erlotinib	Cetuximab	Gefitinib
Any rash	75%	70% (382 of 548 patients)	37%
Grade 3/4 rash	9%	10%	2%



FIGURE 2. Nail fungus with paronychia in a patient taking erlotinib



FIGURE 3. Fingertip splitting



FIGURE 4. Scalp rash in a patient taking erlotinib, 150 mg, after 3 weeks of therapy

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and be graded but does not describe EGFR inhibitor rash in particular.⁶ The Multinational Association for Supportive Care in Cancer (MASCC) utilized a panel of experts to propose an update to the current scale, a specific EGFR inhibitor-dermatologic grading scale, which incorporates 17 different skin, nail, eye, hair, and oral toxicities that can occur with EGFR inhibitors.⁷ The online version of this article contains a link to that scale.

Nonpharmacologic approaches to the prevention of rash are important and can help patients to maintain autonomy and continue treatment uninterrupted.

- Since the rash tends to be drying, ask the patient to apply a thick, emollient cream to the face and body once or twice a day as soon as the medication is started. Creams tend to be better as lotions are usually thinner and water-based. Also, be sure that the cream is without dyes or fragrances that may irritate the skin.
- Patients who anticipate sun exposure should be instructed to apply a sun block of SPF15 or higher. Note your patient's occupation. If she sits close to a window where the sun may shine on her, or if he drives a truck where the sun is shining on him through the windshield all day, sun protection is especially important.
- Another prevention technique is to take the oral EGFR inhibitors on an empty stomach. Taking them with food will increase their bioavailability, thus causing heightened side effects.
- Nurses should also be aware of concomitant medications that the patient is taking because erlotinib is metabolized via the CYP3A4 pathway in the liver. Potent CYP3A4 inhibitors, such as certain antifungals, clarithromycin, and grapefruit juice, can dramatically increase the plasma levels of erlotinib, which can in turn worsen the side effects.

Treatment of the papulopustular rash can be challenging. No randomized trials of treatment have been performed, and in the absence of clinical trial data, best practice guidelines have been put forth, as have data from pre-emptive trials and strategies documented by dermatology clinics.

The first guidelines published for EGFR inhibitor rash management came from a group of dermatologists, oncologists, pharmacists, and oncology nurses who met at a summit in 2006 to formulate a "best practice" algorithm. This algorithm utilizes a step-wise approach based on severity of the rash, using topical corticosteroids and antibiotics to treat minor rash as well as oral antibiotics and oral corticosteroids if necessary for moderate or severe rashes.⁸ Also published is the work of dermatologist Dr. Mario Lacouture and his experiences in the S.E.R.I.E.S. clinic (Skin and Eye Reactions to Inhibitors of EGFR and kinase).⁹ This approach, again based on clinical

practice, recommends lower doses of synthetic tetracycline (STCN) antibiotics along with pimecrolimus cream (Elidel), an immunomodulator cream, for mild/moderate rashes. It recommends STCNs at higher doses with stepwise addition of corticosteroids for more severe rashes.

Another approach is to prevent the rash by using these medications when EGFR inhibitor therapy is initiated. Most rash prophylaxis trials have involved panitumumab (Vectibix), a monoclonal antibody that has the highest rate of grade 3/4 rash among the EGFR inhibitors. The STEPP trial compared preventive rash therapy using oral doxycycline and topical hydrocortisone 1% cream versus reactive treatment of EGFR inhibitor rash in patients receiving panitumumab for metastatic colorectal cancer.¹⁰ Patients who received the prophylactic therapy had a 50% reduction in grade 2 or higher rash compared to the patients who were treated reactively.¹⁰ Patients in the preventive therapy arm also had improved quality of life compared to those in the reactive arm. Since rash can correlate with disease response and survival in some EGFR inhibitor cancer trials, there is concern that preventing the rash from developing could also make the drug less efficacious. Based on the STEPP trial results, future study of rash prevention therapies and any possible correlation with survival is warranted.

TREATMENT STRATEGIES FOR OTHER SIDE EFFECTS

The second most common side effect of EGFR inhibitors is diarrhea. This adverse reaction is usually very manageable, although elderly patients may be at greater risk for dehydration and should be monitored closely. Patients should be advised to avoid spicy or greasy foods and to follow the BRAT (bananas, rice, applesauce, toast) diet if loose stools occur. OTC medications such as loperamide (Imodium) can relieve the diarrhea. If OTC products are not effective, a prescription medication such as diphenoxylate/atropine (Lomotil) can offer stronger relief. Reduction in EGFR inhibitor dose may be necessary if the diarrhea persists. A patient who is having persistent diarrhea should be monitored for electrolyte imbalances, such as low magnesium and potassium levels.

Magnesium wasting is seen mostly with cetuximab and is less common with the EGFR TKIs. This side effect is

certainly exacerbated when there is simultaneous diarrhea, but it can occur independent of loose bowels. Checking serial magnesium levels is important. Symptoms of hypomagnesemia are muscle weakness, confusion, decrease in reflexes, and cardiac arrhythmias, although these symptoms are usually present only when magnesium levels are dangerously low. The best way to replenish magnesium is to give it intravenously, 1 g over 15 minutes. Higher amounts of magnesium given IV need to be run slower because of cardiac

Prevention and management of EGFR inhibitor side effects can allow the patient to remain on therapy at either a full or decreased dosage.

safety concerns. Oral repletion is less effective but is often done for convenience. The most common form prescribed is usually magnesium oxide, though magnesium gluconate and magnesium chloride are also available. Oral replacement dosing is often limited by diarrhea as a side effect.

After longer-term use of EGFR inhibitors, other dermatologic effects can occur. Inflammation and soreness around the nail beds, known as paronychias, are difficult to treat, but topical antibiotics or antifungals, or soaks with Epsom salts or diluted betadine, can sometimes help (Figure 2). Oral antibiotics may work, especially if erythema or pus is present. Prevention is key. Teaching patients up front to keep nails clean and trimmed can hopefully prevent this complication. Fingertip splitting from very dry skin is also a later side effect (Figure 3). Prescription-strength urea moisturizers and glues such as Superglue or Liquid Bandaid can be utilized for treatment. Also, be sure that the patient is not exposing the fingers to extreme temperatures or friction that may exacerbate the splitting or paronychias.

Alopecia or hair thinning can occur from EGFR inhibitor use. The alopecia is usually partial rather than complete, as occurs with chemotherapy; however, the hair can become brittle and fall out in clumps. This side effect can be worse if the papulopustular rash is present on the scalp (Figure 4). Therapeutic shampoos, such as OTC t-gel shampoos or prescription-strength shampoos such as fluocinonone acetone (Capex), can help moisturize the scalp. The eyelashes and eyebrows can also grow long and brittle, sometimes curling inward toward the eye. To avoid corneal abrasions, the eyelashes should be kept trimmed.

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SEE THE ONLINE VERSION OF THIS ARTICLE TO LINK TO

The Multinational Association for Supportive Care in Cancer (MASCC) EGFR inhibitor-dermatologic grading scale
http://data.memberclicks.com/site/mascc/MASCC_MESTT.pps

CONCLUSION

EGFR inhibitors are a mainstay in the treatment of lung cancer, and oncology nurses play a vital role in their effective use. Prevention and management of EGFR inhibitor side effects can allow the patient to remain on therapy at either a full or decreased dose, an important goal if the patient's cancer is responding well to treatment. Educating patients about strategies to prevent and manage EGFR inhibitor side effects is a key factor to helping them maintain body image while on these medications and remain adherent to therapy. ■

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