CHAPTER 2

Managing Side Effects of EGFR Inhibitors

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Managing Side Effects of EGFR Inhibitors (Cetuximab, Panitumumab, Gefitinib, Erlotinib)

The epidermal growth factor receptor (EGFR) is a transmembrane protein that plays a key role in signal transduction pathways regulating cellular proliferation, survival, and differentiation.\(^1,2\) EGFR is a member of the ErbB family, also known as the human epidermal growth factor receptor (HER) family.\(^3,4\) Dysregulation of EGFR activation has been associated with various processes in tumor growth and progression, including angiogenesis, inhibition of apoptosis, and metastasis.\(^2,5,6\) Overexpression of EGFR is common in a wide variety of solid tumors (Table 1)\(^5,7\) and is thought to be an important element in the development and spread of many forms of epithelial malignancy.\(^3,4,6\)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Overexpression of EGFR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>25–77</td>
</tr>
<tr>
<td>Head and neck</td>
<td>80–100</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>30–50</td>
</tr>
<tr>
<td>Non-small-cell lung cancer</td>
<td>40–80</td>
</tr>
<tr>
<td>Breast</td>
<td>14–91</td>
</tr>
<tr>
<td>Renal carcinoma</td>
<td>50–90</td>
</tr>
<tr>
<td>Ovarian</td>
<td>35–70</td>
</tr>
<tr>
<td>Glioma</td>
<td>40–63</td>
</tr>
<tr>
<td>Bladder</td>
<td>31–48</td>
</tr>
</tbody>
</table>

Two types of EGFR inhibitors are used in the treatment of solid tumors.\(^3\) Monoclonal antibodies (mAbs) bind to the extracellular domain to downregulate surface EGFR expression, prevent ligand binding, and interrupt the downstream signaling cascade. These actions promote tumor apoptosis, inhibit tumor angiogenesis, and may stimulate immunologic response.\(^3,5,8\) The two key mAb EGFR inhibitors approved for treatment of solid tumors are cetuximab and panitumumab.

The other EGFR inhibitors, gefitinib and erlotinib, are oral tyrosine kinase inhibitors (TKIs). These small molecules bind to the intracellular domain of EGFR to inhibit phosphorylation of TK, thereby disrupting the downstream signaling resulting from EGFR ligand binding.\(^3,8\)

**Current and Future Uses**

**Cetuximab**

A chimeric IgG1 mAb, cetuximab has been approved for the treatment of

- EGFR-expressing metastatic colorectal cancer (mCRC)
  - As monotherapy after failure of both irinotecan- and oxaliplatin-based chemotherapy\(^9\)
  - As monotherapy for those intolerant to irinotecan-based chemotherapy\(^9\)
As combination therapy with irinotecan in patients refractory to irinotecan-based chemotherapy\(^9\)

- Patients are eligible only if their tumors are determined to be EGFR-expressing. \(^9\) (Kits are available that test for the presence of EGFR in colon tissue samples.\(^{9,10}\)) This testing is usually done by the pathology laboratory and results appear on the pathology report.

- Recommended dosage for cetuximab IV infusion, both in combination with irinotecan and as monotherapy, is 400 mg/m\(^2\) as a 120-minute loading dose, followed by an ongoing weekly maintenance dosage of 250 mg/m\(^2\) infused over 60 minutes.\(^9\) Maximum infusion rate is 10 mg/minute\(^9\)

- Squamous cell cancer of the head and neck (SCCHN)
  - In combination with radiation therapy (RT) for initial treatment of locally or regionally advanced SCCHN\(^9\)
  - As monotherapy for recurrent or metastatic SCCHN when prior platinum-based therapy has failed\(^9\)
  - Evidence of EGFR expression is not required because virtually all SCCHNs are EGFR positive\(^9\)
  - Recommended dosage is the same as for mCRC\(^9\)
  - When administered concurrently with RT, the first dose is given 1 week prior to initiation of RT, and the weekly dosage is continued for the duration of RT (6–7 weeks). In clinical studies, infusions were administered 1 hour before RT\(^9\)
  - When administered as a single agent for treatment of recurrent or metastatic SCCHN, weekly dosages are continued until disease progression or unacceptable toxicity\(^9\)

**Panitumumab**

A fully human IgG2 kappa mAb,\(^{11,12}\) panitumumab, given as an infusion, has been approved as monotherapy for EGFR-expressing mCRC following progression on prior chemotherapy regimens.\(^{11}\)

- Recommended dosage is 6 mg/kg intravenous infusion administered over 60 minutes every 2 weeks. Doses of more than 1000 mg should be administered over 90 minutes\(^{11}\)

Panitumumab is not indicated for use in combination with chemotherapy. Such combinations may result in reduced efficacy and increased severe toxicities.\(^{11}\)

**NOTE regarding K-ras Testing:** Tumors with K-ras mutations do not respond well to cetuximab\(^{13}\) and panitumumab.\(^{14}\) Therefore, K-ras testing may now be considered as a means for selecting appropriate candidates for these agents.

**Erlotinib**

A human TK EGFR inhibitor administered in tablet form, erlotinib hydrochloride is approved

- As monotherapy for treatment of patients with locally advanced or metastatic non–small-cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen\(^{15,16}\)
o Recommended dosage: 150 mg taken at least 1 hour before or 2 hours after eating. Continue treatment until disease progression or unacceptable toxicity\textsuperscript{15}

- In combination with gemcitabine for first-line treatment of locally advanced, unresectable, or metastatic pancreatic cancer\textsuperscript{15,16}
  - Recommended dosage: 100 mg daily, taken at least 1 hour before or 2 hours after eating. Continue treatment until disease progression or unacceptable toxicity\textsuperscript{15}

**Gefitinib**

Gefitinib was the first TKI to be approved, and its initial approval included an indication for treatment of NSCLC in patients who were refractory to established chemotherapy treatments.\textsuperscript{17} However, concerns about the safety of gefitinib arose when numerous patients with NSCLC in Japan reportedly died from interstitial lung disease (ILD) during treatment.\textsuperscript{18} Subsequent clinical trials failed to demonstrate a significant survival benefit from treatment with gefitinib, whether in combination with chemotherapy,\textsuperscript{19,20} as maintenance therapy,\textsuperscript{21} or as monotherapy for patients refractory to chemotherapy.\textsuperscript{22} Meanwhile, erlotinib received approval for use in patients with NSCLC. As a result, in 2005 the FDA restricted the approved use of gefitinib to continued treatment of patients with NSCLC who have shown prior benefit from the drug.\textsuperscript{17,23} Since gefitinib is therefore rarely used, the remainder of this chapter focuses on cetuximab, panitumumab, and erlotinib.

There are more than 800 ongoing or recently completed clinical trials investigating the efficacy of cetuximab, panitumumab, erlotinib, and gefitinib as treatments for a wide variety of cancers in a wide variety of settings.

**Side Effects**

Common side effects associated with administration of EGFR inhibitors include\textsuperscript{9,11,15}

- Cutaneous effects
- Constipation\textsuperscript{a}
- Electrolyte depletion/hypomagnesemia\textsuperscript{b}
- Fatigue
- Headache\textsuperscript{a}
- Nausea
- Vomiting
- Diarrhea
- Infection\textsuperscript{a}
- Abdominal pain\textsuperscript{c}
- Anorexia\textsuperscript{d}
- Liver function abnormalities\textsuperscript{d}
Potentially serious reactions associated with administration of EGFR inhibitors include

- Infusion reactions\(^b\)
- Skin rash/dermatologic toxicities
- Cardiovascular and pulmonary toxicities
- Severe electrolyte depletion/hypomagnesemia\(^b\)
- Severe diarrhea
- Hepatic failure/hepatorenal syndrome\(^d\)
- Renal failure\(^e\)
- Sepsis\(^a\)

\(^a\)Associated with cetuximab
\(^b\)Associated with mAb EGFR inhibitors
\(^c\)Associated with panitumumab and erlotinib
\(^d\)Associated with erlotinib
\(^e\)Associated with cetuximab and erlotinib

Side effects are graded on a scale of 1 to 4 according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events.

**Managing Selected Side Effects**

**Infusion Reactions**

Rare severe infusion reactions have occurred with administration of cetuximab and, less frequently, with panitumumab. Infusion reactions with mAbs may be related to immune responses to murine components of the antibody. Rates of infusion reactions may be lower with panitumumab because it is a fully human mAb. Infusion reactions occurred in 15% to 21% of cetuximab-treated patients overall, and severe reactions occurred in 2% to 5%, with one fatality.\(^9\) The incidence of infusion reactions with panitumumab was 4% overall, and severe infusion reactions developed in approximately 1%; no deaths have been reported.\(^11\) Symptoms of infusion reaction may include pyrexia, chills, rigors, dyspnea, bronchospasm, angioedema, urticaria (hives), and changes in blood pressure.\(^9,11\) Hypersensitivity reactions have been reported at increased frequency among residents of the southeast United States as compared with other areas.\(^24\)

Severe reactions most commonly (90%) occur with initial infusion, but some patients have experienced severe reactions for the first time on later infusions.\(^9\) Severe reactions may be characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, hypertension or hypotension, anaphylaxis, loss of consciousness, and/or cardiac arrest.\(^9,11\)

To manage infusion reactions in patients treated with cetuximab or panitumumab, clinicians should

- Be prepared to treat infusion reactions. Early recognition and prompt intervention are key to managing infusion reactions
  - Standing orders should be in place to enable rapid response
Appropriate therapy may include epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and/or oxygen. Resuscitation equipment should be immediately available.

- Premedicate with H₁ antagonist (e.g., 50 mg diphenhydramine) IV 30 to 60 minutes before first cetuximab dose. Premedication before subsequent doses is at clinician’s discretion and is based on presence/severity of prior infusion. Prophylactic antihistamine treatment did not uniformly prevent severe reactions in clinical trials. Prophylactic treatment has not been routinely recommended with panitumumab.

- Check and record vital signs immediately before infusion, regularly during infusion (every 5–15 minutes), and after infusion.

- Monitor patients for 1 hour after infusion; longer for patients who have experienced reactions.

- According to the prescribing information, mild or moderate reactions can be managed by reducing the infusion rate by 50%. However, some sources recommend immediate discontinuation at the first sign of a reaction with continuation at a reduced dose after symptoms have resolved.

- In the case of mild to moderate infusion reaction, infusion may be resumed at the reduced rate once symptoms have resolved.

- If a severe reaction occurs, immediately halt treatment and keep patients under observation.

Diarrhea

Diarrhea has been noted as a side effect of all EGFR inhibitors, especially erlotinib. In clinical trials of cetuximab and panitumumab, diarrhea occurred more frequently when those drugs were administered in combination with conventional chemotherapy regimens known to be associated with diarrhea. For example, in one trial, 21% of patients in the cetuximab plus irinotecan arm experienced grades 3 to 4 diarrhea compared with ~2% in the cetuximab-alone arm. Similarly, in one small trial (N = 19), 58% of patients treated with panitumumab in combination with IFL (irinotecan, bolus 5-fluorouracil [5-FU], and leucovorin) experienced grades 3 to 4 diarrhea. In part 2 of that study (N = 24), 25% of those treated with panitumumab in combination with FOLFIRI (irinotecan, infusional 5-FU, and leucovorin) experienced grade 3 diarrhea.

In contrast to findings with the mAbs, diarrhea is one of the most common adverse reactions observed with erlotinib. In a study of erlotinib as single-agent treatment of NSCLC, 55% of treated patients experienced diarrhea compared with 19% in the placebo group. Moreover, 6% of erlotinib-treated patients experienced severe diarrhea (grades 3–5) compared with <1% in the placebo group. Diarrhea resulted in dose reductions in 5% of patients in the erlotinib arm of that trial.

For management of diarrhea in patients treated with EGFR inhibitors:

- Nurses should ask patients to describe their bowel function before treatment in order to establish a baseline with which to compare bowel function (diarrhea) on therapy.
Grade 1 = increase of <4 stools/day over baseline; grade 2 = increase of 4 to 6 stools/day or nocturnal stools; grade 3 = increase of ≥7 stools/day or incontinence or need for parenteral support for dehydration; grade 4 = hemodynamic collapse or need for intensive care

Patients who have had intra-abdominal pelvic surgery, gastrointestinal primary tumor or metastasis, or nonmalignant comorbidities may have baseline bowel activity that includes numerous soft or liquid stools/day

Guidelines for managing chemotherapy-induced diarrhea may also apply to diarrhea associated with targeted therapies

- Loperamide 4 mg PO followed by 2 mg every 4 hours or 2 mg every 2 hours
  - Reassess 12 to 24 hours later. If diarrhea is resolving, discontinue loperamide after 12-hour diarrhea-free interval. Unresolved diarrhea may warrant stool culture and additional treatment

- For loperamide-refractory patients
  - If refractory for >24 hours, fever is present, or ANC <500 cells/μL, administer oral fluoroquinolone or other adequate antibiotics
  - If refractory for >48 hours, stop loperamide; hospitalize patient, and administer IV fluids
  - Octreotide 100 to 150 μg TID SC or 25 to 50 μg/hour with dose escalation up to 500 μg for loperamide-refractory or complicated cases of diarrhea
  - Tincture of opium
    - Deodorized tincture of opium: 0.6 mL QID to 10 to 15 drops in water every 3–4 hours
    - Camphorated tincture of opium (paregoric): 1 tsp (5 mL) in water every 3–4 hours

- Advise patients to follow recommended dietary guidelines for diarrhea
  - Maintain adequate liquid intake and consumption of liquids at room temperature. Avoid beverages containing lactose, caffeine, or alcohol, and large quantities of hyperosmotic beverages (eg, fruit juice, sweetened fruit drinks)
  - Drink enough fluids to replace what is lost in addition to the recommended daily amount
  - Fluid replacement should not be achieved through just water because this can lead to hyponatremia and hypokalemia. Replacement fluids should contain some sugar and salt (eg, broth, Gatorade®, soft drinks with some of the carbonation removed)
  - Avoid foods that exacerbate diarrhea (eg, raw fruits and vegetables; whole grain breads; nuts; popcorn; skins; seeds; legumes; and greasy, fried, high-fat foods)
  - Increase consumption of foods that bulk stools (eg, applesauce, oatmeal, bananas, rice, noodles, skinned turkey or chicken, white toast, well-cooked eggs, canned or cooked skinless fruit, mashed potatoes), and replete electrolytes (eg, bananas, peach nectar, apricot nectar, oranges, potatoes)
  - Assess for signs of dehydration (eg, dry mucosal membranes, decreased urination, etc)
Electrolyte Abnormalities

Electrolyte depletion has been observed in patients taking cetuximab or panitumumab. In clinical trials of cetuximab, 55% of patients developed hypomagnesemia, which was severe in 6% to 17%. Hypomagnesemia and electrolyte abnormalities occurred days to months after the start of therapy.9

- Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, in all cetuximab- or panitumumab-treated patients, but especially those being treated concurrently with RT and who have a history of coronary artery disease, arrhythmia, or congestive heart failure. Monitoring should continue for at least 8 weeks following conclusion of treatment.9
- Administer oral or IV electrolyte repletion when necessary.11

Dermatologic Toxicities

Because EGFR is expressed in epidermal tissues and hair follicles, dermatologic toxicities are extremely common during treatment with EGFR inhibitors, occurring in >50% of treated patients.6 Dermatologic side effects associated with EGFR inhibitors include:

- Rash
- Xerosis (abnormal dryness)
- Pruritus (itching)
- Paronychia (inflammation around the nail)
- Alopecia (baldness)
- Trichomegaly (excessive growth of eyelashes)
  - Panitumumab has been associated with other ocular toxicities, including conjunctivitis, ocular hyperemia, increased lacrimation, and irritation.11
- Telangiectasia (permanent dilation of pre-existing blood vessels that create small red lesions on skin or in mucous membranes)

Erlotinib has also been associated with alopecia and hirsutism.15

The most common symptom is a papulopustular eruption (Figure 1), which typically appears on the face, upper chest, and back. Symptoms usually develop in the first 2 weeks of treatment and often, although not always, resolve within 4 to 6 weeks.
Although most cases of rash are mild to moderate in severity (grades 1–2), severe rashes (grades 3–4) do occur and can be complicated by infection.\textsuperscript{9,11} For example, in a clinical trial of patients with SCCHN, 87\% of those treated with cetuximab in combination with RT developed rash, compared with 10\% of those treated with RT alone. Severe rash occurred in 17\% of patients in the cetuximab plus RT arm, versus 1\% in the RT-alone arm.\textsuperscript{9} In a trial of patients with NSCLC, 75\% of those treated with erlotinib developed rash, 8\% of which were grade 3 and <1\% of which were grade 4. In contrast, 17\% of those in the placebo group developed rash, none of which was grade 3 or 4.\textsuperscript{15} Several studies have suggested that the appearance and severity of rash is a sign of effective tumor response to EGFR treatment, but such an association has not been confirmed.\textsuperscript{31,34} Even mild EGFR rashes can significantly impact quality of life, sometimes to the point that the patient withdraws from therapy. Dose reductions or interruptions of treatment often result, thus jeopardizing treatment efficacy.\textsuperscript{6,32}

General steps to reduce the risk of dermatologic toxicities during treatment with EGFR inhibitors include

- Be proactive about minimizing rash in advance, and monitor patients’ conditions to facilitate early detection\textsuperscript{35}
- Educate patients prior to treatment to prepare them psychologically and encourage them to institute prophylactic measures when necessary\textsuperscript{35}
• While educating patients, point out areas around the nails that might become infected. At the same time, check patients’ nails for visual signs of nail biting or cuticle picking, which might increase risk of infection. Nail condition should be assessed before and after treatment.

• In populations with high rates of diabetes, foot care and assessment is especially important.

• Refer to a dermatologist as needed.

• Recommend patient-oriented websites that provide information on controlling EGFR-related dermatologic toxicities. Examples include:
  - [http://www.cancer.org/docroot/MBC/content/MBC_2_3x_Skin_Changes.asp?sitearea=MBC](http://www.cancer.org/docroot/MBC/content/MBC_2_3x_Skin_Changes.asp?sitearea=MBC)
  - [http://www.cancer.net/patient/Diagnosis+and+Treatment/Treating+Cancer/Managing+Side+Effects/Skin+Reactions+to+Targeted+Therapies](http://www.cancer.net/patient/Diagnosis+and+Treatment/Treating+Cancer/Managing+Side+Effects/Skin+Reactions+to+Targeted+Therapies)

• Directly advise patients of the following measures:
  - Keep skin, including hands and feet, clean and moist. Use hypoallergenic, alcohol- and perfume-free moisturizers (eg, Aveeno®, Eucerin®, Vaseline®).³⁵,³⁶
  - Avoid shampoos, soaps, lotions, and laundry products that include perfumes and dyes. Bath or shower oils are preferred³³,³⁵,³⁶
  - Although EGFR-related rash may look like acne, it is not acne and should not be treated as if it were (and clinicians should not refer to it as such). If it occurs, do not use antiacne preparations, such as those that contain benzoyl peroxide or retinoids, which can exacerbate rash by drying the skin³⁶
  - EGFR-associated rash can be concealed with a hypoallergenic cosmetic (eg, Dermablend®). A gentle makeup remover (eg, Dove®, Neutrogena®) should be used³⁷
  - Wear broad-brimmed hats and other protective clothing outside to minimize sun exposure.⁶,⁹,¹¹,³⁵,³⁶ Use sunblock products containing zinc oxide or titanium dioxide.⁶,³⁵,³⁶ SPF should be 30 or higher³⁶
  - Keep fingernails and toenails clean and trimmed. Avoid biting nails, pushing back cuticles, tearing skin around nail bed, and artificial nails. Wear gloves when washing dishes or using cleansers.

Formal evidence-based modalities for the treatment of EGFR-related rash have not been established.⁶,³³,³⁵,³⁶ Anecdotal evidence suggests that the strategies shown in Table 2⁶,⁹,³⁸ may be useful in the management of skin rash.
| Mild rash | Treat macular rash topically with hydrocortisone cream or lotion  
Treat pustular rash with clindamycin gel (isolated lesions) or lotion (multiple areas)  
Reassess condition after 2 weeks. If rash fails to improve, employ treatment recommendations for moderate rash |
| Moderate rash | Continue application of hydrocortisone cream or lotion or clindamycin gel, or apply pimecrolimus cream  
When pustules are present, prescribe a course of oral antibiotics (eg, minocycline hydrochloride, trimethoprim, sulfamethoxazole)  
For pruritis, use topical and/or oral antihistamines (eg, diphenhydramine, hydroxyzine)  
Reassess condition after 2 weeks. If no improvement, initiate treatment for severe rash |
| Severe rash | Dose reduction of EGFR inhibitor (described on page 12)  
Oral steroids for macular rash and oral antibiotics for pustular rash  
Continue application of topical creams; however, use of topical corticosteroids is not recommended for treatment of severe rash  
If ulcerative lesions develop, consider a barrier protection (eg, silver sulfadiazine ointment)  
Monitor patients for inflammatory or infectious sequelae, and treat appropriately when necessary |
In addition to the measures listed in Table 2, referral to a dermatologist may be appropriate. The prescribing information for cetuximab, panitumumab, and erlotinib all recommend dosage reductions in the event of severe (grade 3 or 4) dermatologic reactions.

- **Cetuximab**: delay infusions by 1 to 2 weeks and steadily decrease the standard dose of 250 mg/m² to 200 mg/m² at the second occurrence and 150 mg/m² at the third occurrence. Failure to improve at any stage or a fourth occurrence should result in discontinuation of treatment.

- **Panitumumab**: withhold administration until toxicity improves to ≤ grade 2. Discontinue treatment if improvement does not occur within 1 month, or if toxicities recur. If rash improves after no more than two infusions are withheld, treatment can be resumed at 50% of the original dose, steadily increasing in 25% increments of the original dose until reaching recommended dosage (6 mg/kg).

- **Erlotinib**: reduce dose in 50-mg decrements or interrupt therapy as necessary.

### Cardiovascular Toxicities
EGFR inhibitors have been associated with rare but potentially fatal cardiovascular events. For example, in a trial of cetuximab plus RT for treatment of SCCHN, four (2%) of 208 patients in the cetuximab arm experienced cardiopulmonary arrest and/or sudden death, compared with none of the 212 patients treated with RT alone. Three of the four patients who died had prior histories of coronary artery disease. Severe (grade 3 or 4) hypomagnesemia has been observed in small percentages (2%) of patients treated with panitumumab. Rare occurrences of myocardial infarction/ischemia and cerebrovascular accident (2.3% for both) have been observed in clinical trials of erlotinib combined with gemcitabine for treatment of pancreatic cancer. More frequent, but still rare, cases of venous thrombosis (3.9%) were also observed in that trial. Potential reversibility of these effects is unknown.

Many clinical trials of EGFR inhibitors excluded patients with pre-existing cardiac conditions. Furthermore, clinical trials are of limited duration, whereas, in community settings, many targeted agents are given chronically over longer periods of time. As these drugs are used by more community-based patients, it is likely that rates of cardiotoxicity will be higher than previously reported, and the cumulative effects of these agents on organs, such as heart and lungs, will be determined. While we lack data on some of the newer agents, we are learning from longer-term side effects studied in other targeted therapies in similar classes (eg, trastuzumab and imatinib).

Suggested management strategies include

- Assess pre-existing cardiopulmonary conditions or co-morbidities (eg, diabetes) that could increase the risk of cardiotoxicity or pulmonary toxicity in patients receiving EGFR inhibitors
  - Carefully consider use of cetuximab in combination with RT in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias
- Treatment of cardiovascular toxicity should be in accordance with the standard of care for the specific cardiac abnormality
**Pulmonary Toxicities**

Rare cases of ILD have been reported in patients treated with cetuximab\(^9\) and erlotinib,\(^{15}\) while rare cases (<1%) of pulmonary fibrosis have been reported in patients treated with panitumumab.\(^{11}\) In one trial of pancreatic cancer patients, the incidence of ILD-like events (eg, pneumonitis, radiation pneumonitis, interstitial pneumonia, obliterative bronchiolitis, acute respiratory distress syndrome, lung infiltration, and pulmonary fibrosis) was 2.5% among those treated with erlotinib combined with gemcitabine, compared with 0.4% with gemcitabine alone. However, in a study of erlotinib in patients with NSCLC, there was no difference in the incidence of ILD-like events between treatment and control groups, and the overall incidence of ILD events across all erlotinib studies has been approximately 0.7%\(^{15}\).

Symptoms of ILD have appeared as early as 5 days into therapy and as late as >9 months after starting treatment.\(^{15}\) Confounding or contributing factors were identified in many cases.\(^{15}\) Early symptoms may include dyspnea and fever. Symptoms usually resolve after therapy is discontinued.\(^{25}\)

For management of pulmonary events associated with EGFR inhibitors

- Monitor patients for new symptoms of ILD or acute exacerbation of pre-existing lung disease and investigate further if such symptoms appear
  - Symptoms in NSCLC patients treated with erlotinib will likely be associated with pre-existing conditions, including lung tumors, concomitant/prior chemotherapy, prior RT, pre-existing parenchymal lung disease, and pulmonary infections\(^{15}\)
  - Use high-resolution computed tomography and pulmonary function tests to diagnose ILD\(^{25}\)
- If significant new symptoms of pulmonary distress appear (eg, dyspnea, cough, fever), or if existing conditions progress precipitously, discontinue EGFR inhibitor pending evaluation and treatment, and institute appropriate therapy as needed\(^{15}\)
- Discontinue treatment in any patient who develops ILD, pneumonitis, or lung infiltrates\(^9,^{11}\)
- Treat respiratory symptoms with methylprednisolone\(^{25}\)

**Hepatic Failure/ Hepatorenal Syndrome**

Liver function test abnormalities have been reported in patients taking erlotinib.\(^{15}\) They were usually associated with liver metastases, and were transient.\(^{15}\) However, rarely, these toxicities were severe, and erlotinib has been associated with cases of hepatic failure and hepatorenal syndrome, some of which have been fatal.\(^{15}\) Recommended management strategies are

- Periodically monitor liver functions (ie, ALT, AST, bilirubin, alkaline phosphatase)\(^{15}\)
- If liver functions worsen, interrupt or reduce erlotinib dose\(^{15}\)
- Interrupt/discontinue erlotinib if\(^{15}\)
  - Total bilirubin >3 X ULN
  - Transaminases >5 X ULN
- If patient is dehydrated (especially if there are concomitant risk factors for renal failure), interrupt erlotinib and intensively rehydrate patient\(^{15}\)
Drug Interactions

No drug interactions are listed in the prescribing information for cetuximab or panitumumab.9,11

Erlotinib is metabolized mainly by the CYP3A4 enzyme and, to a lesser extent, by CYP1A2 and CYP1A1.15 Therefore, it should be used with caution in combination with CYP3A4 inhibitors and inducers. CYP3A4 inhibitors may slow metabolism of erlotinib. For example, use of erlotinib with the CYP3A4 inhibitor ketoconazole was shown in one study to increase erlotinib area under the curve (AUC) by two-thirds.15 Similarly, administration with ciprofloxacin increased erlotinib exposure by 39%.15 In addition to ketoconazole, CYP3A4 inhibitors specifically mentioned in the prescribing information for erlotinib are atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice.15 For other CYP3A4 inhibitors, please refer to the Appendix. Erlotinib dose reductions should be considered if severe reactions occur.15

Erlotinib should also be used cautiously with CYP3A4 inducers, which would speed its metabolism. For example, pretreatment with the CYP3A4 inducer rifampicin can decrease erlotinib AUC by two-thirds to four-fifths.15 If no alternative treatment is available, dosage increases of erlotinib at 2-week intervals, as tolerated and with careful monitoring, are recommended. The maximum studied dosage of erlotinib in combination with rifampicin is 450 mg. Upward dose adjustment should be discontinued immediately upon discontinuation of any CYP3A4 inducer. In addition to rifampicin, CYP3A4 inducers listed in the prescribing information for erlotinib are rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, and St. John’s wort.15 For other CYP34A inducers, see Appendix.

In addition, trough plasma concentrations among current smokers treated with erlotinib for NSCLC were approximately two-fold less than that of former smokers or patients who have never smoked. The prescribing information for erlotinib attributes this difference to induction of CYP1A1 in the lungs and CYP1A2 in the livers of current smokers.15

Bioavailability of erlotinib may be reduced by drugs that affect upper gastrointestinal pH. For example, omeprazole decreased erlotinib AUC by 46%. Dose increases of erlotinib are not effective in compensating for this phenomenon. Concomitant use of erlotinib and proton pump inhibitors should be avoided if possible; antacids may be used instead.15

Concurrent use of erlotinib and warfarin may result in elevations of the international normalized ratio (INR) and increased risk of bleeding. Patients taking both erlotinib and warfarin or other coumarin-derived anticoagulants should be monitored for prothrombin time or INR changes.15

Special Populations

EGFR inhibitors may harm fetal development. They should be administered to pregnant women or to women who may become pregnant during treatment only after careful consideration and after potential risks versus potential benefits have been discussed with the patient. In studies of pregnant cynomolgus monkeys, cetuximab and panitumumab produced no fetal malformations or other
teratogenic effects, but at 1.6 to 4 times recommended human doses of cetuximab, or 1.25 to 5 times recommended human doses of panitumumab, embryolethality and abortion rates were increased.9,11 All patients taking EGFR inhibitors should be advised to use effective contraception. Encourage women who become pregnant during panitumumab therapy to enroll in Amgen’s Pregnancy Surveillance Program by phoning 800-772-6436. Mothers are advised to discontinue nursing during treatment with EGFR inhibitors and for 60 days after treatment has been discontinued.9,11,15

Caution and close monitoring are necessary when administering erlotinib to patients with hepatic impairment. Extra caution is recommended for those with total bilirubin >3 X ULN. In a study of patients with moderate hepatic impairment, 10 of 15 patients died during or within 1 month of erlotinib; six of these patients had total bilirubin levels >3 X ULN. Because erlotinib is cleared mainly by the liver, exposure to the drug may be increased in such patients. However, patients with moderately impaired hepatic function (Child-Pugh B) had similar erlotinib exposure compared with those who had adequate hepatic function.15 In addition, liver test abnormalities and hepatic failure have been observed across patient populations in clinical trials. Periodic liver tests (eg, measurement of transaminases, bilirubin, alkaline phosphatase) are recommended. Interrupt or discontinue erlotinib when abnormalities are severe (eg, doubling of total bilirubin and/or tripling of transaminases if pretreatment levels were normal).15
References


Chapter 2. Managing Side Effects of EGFR Inhibitors


