Nursing Management of Epidermal Growth Factor Receptor Inhibitor–Induced Toxicities

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New drug technologies can pose a challenge for nurses, whether it is by educating patients about potential side effects or by helping them deal with sequelae for which there has been little research. Epidermal growth factor receptor (EGFR) inhibitors are new, targeted cancer therapies that are being prescribed with more frequency. Common side effects of EGFR inhibitors include skin rash and diarrhea. An outline of the typical manifestations of EGFR-inhibitor side effects and how nurses can participate in their management to maximize quality of life and treatment adherence follows. Managing side effects is critical to improving tolerance, and failure to manage side effects can lead to treatment cessation. Patient education prior to treatment initiation, as well as ongoing support, is essential to maintaining adequate control of side effects.

EGFR over-expression has been linked to the conversion of normal cells to malignant cells (Toffoli et al., 2007). The identification of epidermal growth factor (EGF) as important in the growth, angiogenesis, anti-apoptosis, and metastasis of some tumor types has resulted in the development of cancer therapies that target EGFR receptors. A number of EGFR inhibitors currently are being used, including erlotinib, cetuximab, panitumumab, and gefitinib.

EGFR inhibitors work by interrupting the pathway that uses EGF to promote tumor growth and metastasis. One mechanism is tyrosine kinase inhibition, in which the drug binds to the EGFR’s intracellular tyrosine kinase and blocks adenosine triphosphate from using the same receptors for malignant cell processes (Dick & Crawford, 2005). Monoclonal antibodies, another approach to EGFR inhibition, block the extracellular component of the receptor, interrupting downstream signaling (Lynch et al., 2007). Malignant cells, which rely on EGF for survival, are particularly vulnerable; growth is arrested and apoptosis occurs when EGFR is inhibited (Lacouture, 2006).

EGFR inhibitors target receptors specifically found in cancer cells and normal epidermal cells. The target specificity of the drugs also is the reason that there tend to be fewer systemic side effects than in common chemotherapy drugs (Lacouture, 2006). The side effects that do occur are a result of the interruption in EGFR in normal cells, which rely on it for development and function, such as stratified squamous epithelium. EGFR is expressed in the undifferentiated keratinocytes of the basal layer of the epidermis and is lost as cells in the layer progress outward and differentiate into cells that ultimately form the stratum corneum, or outermost skin layer (Lacouture). EGFR inhibitors bind to the receptors on the surface of the normal cells in the skin and lining of the digestive tract. When the normal pathway is interrupted by an EGFR inhibitor, several different mechanisms occur to interfere with keratinocyte growth and survival, cell differentiation, attachment, and migration of cells from basal to stratum corneum. This interruption results in inflammation and xerosis, or dryness of the skin. In time, this hyperkeratosis causes a folliculitis, which progresses to a papulopustular rash (Wyatt, Leonard, & Sachs, 2006) that usually occurs on the seborrheic areas, such as the face, arms, and upper trunk (Segaert & Van Cutsem, 2005). Inflammatory reactions and sensitivity to ultraviolet radiation exposure increase in the presence of EGFR inhibitors. Skin reactions often are worse on sun-exposed areas, such as the face, upper chest and back, and dorsal arms. Inflammation in the gastrointestinal tract results in diarrhea.

Complex Management

The pathophysiology and management of EGFR inhibitor–induced skin reactions is complex, and a number of different treatment approaches have been suggested. A recent consensus has been developed on what currently is termed “best practice” to treat these rashes because no randomized studies have been conducted to date (Eaby, Culkin, & Lacouture, 2008). Suggested treatments include antiinflammatory therapy for lower-grade reactions, clindamycin gel and tetracycline for moderate to severe cases (Eaby et al.; Segaert & Van Cutsem, 2005), topical vitamin K (Perez-Soler, Zou, Li, Tornos, & Ling, 2006) and topical corticosteroids, antibiotics, and oral corticosteroids (Eaby et al.; Perez-Soler, 2004). Of note, it has been shown in two large trials that the severity of side effects (particularly rash) experienced with EGFR-inhibitor therapy positively correlates with the effectiveness of the
treatment, with an increased response rate and overall survival associated with grade 2 or higher rash (Wacker et al., 2007).

The papulopustular rash associated with EGFR-inhibitor therapy is very common, tends to arise within 5 to 8 days of treatment initiation, and reaches its maximum severity within 2 to 3 weeks. It generally resolves within a few weeks of treatment discontinuation (Segaert & Van Cutsem, 2005) (see Table 1).

Diarrhea occurs in more than 50% of patients on EGFR inhibitors and generally is easily controlled with loperamide (Gentech, 2007). Although diarrhea can be a debilitating side effect, it has been less studied (in association with EGFR medications) than the cutaneous effects.

### Nursing Guidelines for Managing Side Effects

The severity of rash is correlated with greater response to EGFR inhibitors (Perez-Soler et al., 2004; Wacker, 2007). Patients should be informed of this information with the objective of improving their subjective tolerance of the therapy and, possibly, treatment adherence.

Mild-to-moderate rash can be safely covered with makeup (Dick & Crawford, 2005). Good skin care with hypoallergenic cleansers also is essential. Colloidal oatmeal can be used with good effect and minimal toxicity (Alexandrescu, Vaillant, & Dasanut, 2007). Moisturizers should be used from the initiation of treatment (Eaby et al., 2008; Lynch et al., 2007).

As the rash tends to be worse in areas exposed to sunlight, using sunscreen (SPF greater than 15) and avoiding sun exposure (using a wide-brimmed hat and wearing long sleeves) is recommended (Eaby et al.; Lynch et al.).

For more severe rash (grade 3 or 4), topical corticosteroids, antibiotics, antihistamines, and oral analgesics can be used (Dick & Crawford, 2005; Lynch et al., 2007; Segaert & Van Cutsem, 2005; Wyatt et al., 2006; Yamamoto, Viale, & Zhao, 2004). A significant risk of secondary infection comes with alteration in skin integrity. Infections must be monitored and treated with oral antibiotics such as tetracyclines (which also have antiinflammatory properties) (Dick & Crawford, 2005). Swabs should be taken to assess for bacterial, viral, or fungal infections, although most of the papulopustular lesions will likely be sterile (Wyatt et al.).

In severe cases, some patients may choose an interruption in treatment for personal reasons, such as important social events. Skin reactions tend to improve within four weeks of stopping treatment (Lynch et al., 2007; Segaert & Van Cutsem, 2005) and tend to be less severe when treatment is resumed at a lower dose (Eaby et al., 2008). The addition of immunomodulating agents, such as tacrolimus or pimecrolimus, may be used topically (Lynch et al.); however, care needs to be taken with these products because of possible immunosuppressive effects (Eaby et al.).

### Recommendations

Thorough assessment at regular intervals, with appropriate grading of side effects and related quality of life, is central to the nursing care of patients on EGFR inhibitors. Good skin care should be part of the medication education done prior to treatment initiation. Patients should be encouraged to use hypoallergenic cleansers, moisturizers, and makeup to cover mild rashes. Reassessment is required at least every two to three weeks in the clinic or by patient report, and topical corticosteroids and colloidal oatmeal can be purchased without prescription for mild reactions. If the rash progresses to a more severe grade, pustule swabbing is indicated to rule out a bacterial infection, followed by the use of stronger topical corticosteroids, topical antihistamines, and topical or systemic antibiotics. For severe or debilitating rash, a treatment holiday, dose reduction, or complete cessation may be considered.

### Table 1. Grading of Skin Reactions

<table>
<thead>
<tr>
<th>GRADING (LYNCH)</th>
<th>GRADING (EABY)</th>
<th>APPEARANCE</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (marginal)</td>
<td>Mild</td>
<td>Localized; xerosis, erythema, occasional pustules</td>
<td>Meticulous skin care and hypoallergenic cleansers</td>
</tr>
<tr>
<td>Grade 2 (mild)</td>
<td>Moderate</td>
<td>Generalized, sterile pustules</td>
<td>Topical corticosteroids, colloidal oatmeal, antihistamines, and antibiotics</td>
</tr>
<tr>
<td>Grade 3 (moderate)</td>
<td>Severe</td>
<td>Generalized, extensive, open areas with crusting, thin skin, severe tenderness, affecting quality of life</td>
<td>Systemic antibiotics, strong topical corticosteroids, immunomodulators, dose reduction</td>
</tr>
<tr>
<td>Grade 4 (severe)</td>
<td>Severe</td>
<td>Exfoliative, ulcerated</td>
<td>Treatment holiday, treatment cessation</td>
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Note. Patients should be assessed by either a healthcare professional or by self-report at least every two weeks to closely monitor rash and sequelae that can occur.

Note. Based on information from Eaby et al., 2008; Lynch et al., 2007.
Diarrhea must be assessed in terms of frequency and severity. Hydration and perianal skin integrity can become issues for patients suffering from severe diarrhea, so skin care and oral hydration are essential. Oral loperamide is recommended at an initial loading dose of 4 mg, with an additional 2 mg dose following each bowel movement. Diarrhea, which is refractory to loperamide, might benefit from codeine or other opioid analgesics. A patient’s existing use of opioids may negate the diarrhea effect of EGFR inhibitors. IV hydration and other antidiarreheal medications (lomotil, atropine, and octreotide) may be considered if diarrhea becomes intolerable. Dietary considerations also can be helpful. Patients should be encouraged to eat mild foods such as toast and crackers and binding foods such as bananas and applesauce (Shah, 2004). Patients also should avoid spicy or fatty foods or foods high in caffeine, fiber, or dairy.

At all stages, quality of life must be balanced against potential or actual treatment effectiveness. Although EGFR inhibitors are related to an increase in survival time, patients will inevitably consider the implications of more time compared against side effects such as diarrhea or painful and disfiguring skin rash, which can limit a patient’s freedom to leave the house. Nurses can provide holistic care to patients by engaging in therapeutic and supportive dialogue and making referrals to psychosocial support services when appropriate.

**Conclusion**

Targeted therapies, such as EGFR inhibitors, are being used with increasing frequency to treat solid tumors and nurses often are called on to assist with the management of associated side effects. Although the severity of cutaneous toxicity seems to be correlated with efficacy in individual patients, the same severity can be sufficiently debilitating so that it affects treatment adherence. Ongoing assessment and early, evidence-based intervention for side effect management can improve quality of life for patients on EGFR inhibitors. Oncology nurses play a significant role in the maintenance of treatment adherence and quality of life for these patients.

**References**


**Spot on tumor markers . . .**

To learn more about dermatologic toxicities related to epidermal growth factor receptor inhibitors, visit www.cancernetwork.com/display/article/10165/62753.