Epidermal growth factor receptor (EGFR) inhibitors have been used to treat a variety of malignancies, including head and neck cancer, non–small-cell lung cancer (NSCLC), pancreatic cancer, and colorectal cancer.1 Examples of drugs that make up this class of targeted medications include cetuximab, panitumumab, necitumumab, erlotinib, gefitinib, osimertinib, and afatinib. One of the most common classwide adverse events associated with these drugs is dermatologic toxicity. Skin reactions associated with EGFR inhibitor therapy may manifest as papulopustular (acneiform) rash, mucositis, xerosis, paronychia, and skin fissures.2

In general, dermatologic adverse events with anti-EGFR therapy are common, with specific types depending on the type of dermatologic reaction. Papulopustular rash is the most common dermatologic adverse event that may occur with EGFR inhibitors, with an incidence of up to 90%.1 This adverse event may vary in degree of severity, and lead to dose adjustments of the EGFR inhibitor in severe cases.

EGFR inhibitor–induced papulopustular rashes can be bothersome to patients, which affects quality of life, psychosocial well-being, and placing patients at risk for secondary skin infections.2 Despite the risks associated with this adverse event, evidence exists that response to treatment is correlated with the grade of severity of the reaction.3

SYMPTOM MANAGEMENT OVERVIEW

EGFR Inhibitor–Associated Papulopustular Rash

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SYMPTOM OVERVIEW

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ETIOLOGY

EGFR is a transmembrane tyrosine kinase receptor that has an important role in the maintenance of the normal physiology of skin. EGFR is expressed by undifferentiated and proliferating keratinocytes within the epidermis, hair follicles, and sweat glands.4 EGFR activation is an essential step in the proliferation, differentiation, and survival of keratinocytes. EGFR is an important target in the treatment of epithelial cancers, because it is often overexpressed. The activation of EGFR in malignancy can inhibit the apoptosis of malignant cells, as well as promote the proliferation, adhesion, and migration of tumor cells.5

The mechanism of EGFR inhibitor–induced papulopustular rash is likely caused by the direct inhibition of EGFR in epithelial cells. The inhibition of EGFR in epithelial cells disturbs the normal function of keratinocytes, leading to increased production of chemokines that recruit inflammatory cells, such as leukocytes and neutrophils, and resulting in an inflammatory response that manifests as a papulopustular rash.1

Papulopustular rash associated with EGFR inhibitors typically presents early in therapy, with most cases developing within the first 2 weeks of therapy.6 The rash usually manifests as pruritic and erythematous papules and pustules.3 Parts of the skin containing higher densities of sebaceous glands, such as the scalp and face (particularly the nose, cheeks, and around the mouth), tend to be more susceptible of rash involvement.4

Although less common, rashes may progress and involve the lower trunk, arms, legs, and buttocks. After discontinuation of EGFR inhibitors secondary to severe dermatologic reactions, rashes usually resolve within 4 weeks. Permanent scarring caused by rashes is unlikely to occur,7 but other long-term effects, such as skin erythema and hyperpigmentation secondary to rash, may arise.2

Table 1 Risk Factors for Rash

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>EGFR Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultraviolet light exposure</td>
<td>Patients using erlotinib who are:</td>
</tr>
<tr>
<td></td>
<td>• Nonsmokers</td>
</tr>
<tr>
<td></td>
<td>• Aged &gt;70 years</td>
</tr>
<tr>
<td></td>
<td>• Fair skin types</td>
</tr>
<tr>
<td></td>
<td>Patients using cetuximab who are:</td>
</tr>
<tr>
<td></td>
<td>• Male</td>
</tr>
<tr>
<td></td>
<td>• Aged &lt;70 years</td>
</tr>
</tbody>
</table>

Several risk factors have been identified that may predispose patients to dermatologic reactions with EGFR inhibitors (Table 1). Exposure to ultraviolet light increases the risk, and patients who have a skin type that is more likely to develop sunburns are at an increased risk for severe papulopustular rashes as a result of anti-EGFR therapy. Papulopustular rash is a dose-dependent adverse event. Patients who receive erlotinib and smoke tobacco during therapy tend to have a reduced risk for dermatologic adverse events, because of enzymatic induction of cytochrome P450 leading to lower drug exposure.

Age plays a less clear role than other factors in the risk for severe papulopustular rash with EGFR inhibitors. Elderly patients with NSCLC who receive erlotinib have had rashes of higher grades than patients; by contrast, younger patients who receive cetuximab for colorectal cancer will have more severe rashes than elderly patients. In addition, severe reactions tend to occur more frequently (up to 17%) with anti-EGFR monoclonal antibodies compared with up to 9% with small-molecule tyrosine kinase inhibitors (TKIs).

The risk for severe, grade ≥3 papulopustular rash may be lower with second-generation TKIs (eg, afatinib) compared with first-generation TKIs (eg, erlotinib). The third-generation TKI osimertinib has a very low (1%) incidence of grade ≥3 papulopustular rash, which may be caused by its higher selectivity to the EGFR T790M mutation associated with malignancy compared with wild-type EGFR that tends to be expressed more in the skin.

### TREATMENT OPTIONS

Prevention is a very important management strategy with EGFR inhibitor–associated papulopustular rashes. Prophylactic and preventive pharmacologic strategies should be used with initiation of EGFR inhibitors in the absence of any contraindications. Preemptive treatment of EGFR inhibitor–induced rashes has been shown to

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Pharmacologic Treatment Options for EGFR Inhibitor–Induced Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Dose&lt;a&gt;</td>
</tr>
<tr>
<td>Hydrocortisone 1%</td>
<td>Twice daily, topical</td>
</tr>
<tr>
<td>Alclometasone 0.05%</td>
<td>Twice daily, topical</td>
</tr>
<tr>
<td>Fluocinonide 0.05%</td>
<td>Twice daily, topical</td>
</tr>
<tr>
<td>Clindamycin 1%</td>
<td>Twice daily, topical</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Daily 20-30 mg orally</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg twice daily, orally</td>
</tr>
<tr>
<td>Minocycline</td>
<td>100 mg once daily, orally</td>
</tr>
</tbody>
</table>


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decrease the incidence of grade ≥2 papulopustular rashes and lessen the potential for this adverse event to affect quality of life.10,11

The Multinational Association of Supportive Care in Cancer has published guidelines to address the proper prevention and treatment of EGFR inhibitor–induced skin reactions (Table 2).2 It is recommended that all patients receive topical and systemic preventive pharmacologic care for the first 6 weeks of therapy with an EGFR inhibitor, because most patients will have a papulopustular rash within this time frame.

Topical preventive care should consist of hydrocortisone 1% cream combined with a moisturizer and sunscreen. During the first 6 weeks of therapy, patients should also receive oral doxycycline 100 mg twice daily or oral minocycline 100 mg once daily. Although the etiology of EGFR inhibitor–induced papulopustular rash is not considered to be bacterial in nature, doxycycline and minocycline are effective in the management of EGFR inhibitor–induced rash, as a result of their intrinsic anti-inflammatory effects.4,12 Doxycycline may be more tolerable than minocycline, particularly in patients with renal impairment.2 However, minocycline is less photosensitizing than doxycycline, and therefore may be a preferred option in patients residing in geographic regions with a high ultraviolet index.

In addition to being effective in the preemptive management of EGFR inhibitor–induced papulopustular rashes, doxycycline and minocycline are effective in the reactive treatment of this adverse event. Topical clindamycin 1% and medium- to high-potency corticosteroids, such as fluorocinonide 0.05% cream and alclometasone 0.05% cream, are recommended medications for the reactive treatment of anti-EGFR–induced rashes.2 These topical and systemic therapies may be used in combination with each other to manage this adverse event.4 Isotretinoin may also be a useful drug for the treatment of EGFR inhibitor–induced rashes; however, its use has not been evaluated in controlled studies.13 Given the limited evidence, low doses of isotretinoin may be best used in refractory cases of papulopustular rash.

CONCLUSION

EGFR inhibitors are a common treatment option for a variety of cancers, and papulopustular rash that frequently occurs with their administration creates a unique challenge for clinicians. Although the incidence and severity of papulopustular rash with EGFR inhibitors may correlate with response to treatment, it is an adverse reaction that can decrease a patient’s quality of life, has psychosocial effects, and can place patients at risk for secondary skin and soft-tissue infections. This particular side effect (ie, papulopustular rash) peaks in incidence and severity early on in therapy, and eventually decreases in severity in approximately 6 to 8 weeks.2 However, EGFR inhibitor–induced rashes may lead to long-term issues, such as erythema and hyperpigmentation of the skin; therefore, proactive and preventive pharmacologic strategies should be used in patients receiving this particular class of drugs.

Author Disclosure Statement

Dr Moore has no conflicts of interest to report.

References


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