HER1/EGFR Inhibitor-Associated Rash: Future Directions for Management and Investigation Outcomes from the HER1/EGFR Inhibitor Rash Management Forum

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Key Words. HER1/EGFR · Rash · Adverse event · Survival · NSCLC · Tyrosine kinase inhibitor · Monoclonal antibody

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the clinical and pathological characteristics of the cutaneous rash secondary to anti-EGFR therapy.
2. Explain the prognostic implications of the cutaneous rash secondary to anti-EGFR therapy.
3. Discuss the treatment of the cutaneous rash secondary to anti-EGFR therapy.

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ABSTRACT

Skin rash associated with HER1/epidermal growth factor receptor (EGFR) inhibitors is common. The lack of clinical and patient guidance for this often chronic and sometimes distressing side effect makes rash management and etiology investigation high priorities. To address this, oncologists and dermatologists with experience with HER1/EGFR inhibitors attended the HER1/EGFR Inhibitor Rash Management Forum. Recommendations include continued analysis of the correlation between rash and clinical outcome and improving the accuracy and reproducibility of...
INTRODUCTION

Over the past 10 years the approach to cancer treatment has changed because of improved understanding of the processes that regulate tumor growth and development. We now have anticancer strategies that inhibit the processes enabling tumors to grow, metastasize, and evade the host's immune system. These targeted strategies promise activity against various tumors at different stages of development, alone or in combination with standard therapies, while avoiding most of the nonspecific toxicities that are common in standard chemotherapy and radiotherapy. Many oncologists hope that in the future these agents will make cancer a manageable chronic disease for many patients.

Initial targets included members of the human epidermal growth factor receptor (HER) family, such as HER1/EGFR and HER2; CD20; molecules involved in angiogenesis, such as vascular endothelial growth factor; cyclooxygenase-2; and abl tyrosine kinase (activated by the bcr/abl translocation). Recently, the U.S. Food and Drug Administration (FDA) approved three agents that inhibit HER1/EGFR: gefitinib (Iressa®; AstraZeneca, Wilmington, DE, http://www.astrazeneca.com), cetuximab (Erbitux™; Bristol-Myers Squibb Company, Princeton, NJ, http://www.bms.com; ImClone Systems Inc., Branchburg, NJ, http://www.imclone.com; Merck, Darmstadt, Germany, http://www.merck.com), and erlotinib (Tarceva™; Genentech Inc., South San Francisco, http://www.gene.com; OSI Pharmaceuticals Inc., Melville, NJ, http://www.osip.com; Hoffmann-La Roche, Basel, Switzerland, http://www.roche.com). The FDA approved gefitinib as third-line monotherapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel chemotherapies, and cetuximab for patients with irinotecan-refractory or intolerant metastatic colorectal cancer (CRC). Recent data from a phase III study of erlotinib HCl, a HER1/EGFR tyrosine kinase inhibitor, show it is the only HER1/EGFR-targeted agent to improve survival compared with placebo in patients with advanced/refractory NSCLC [1].

Many HER1/EGFR-targeted agents are being developed, mainly tyrosine-kinase inhibitors or monoclonal antibodies (Table 1). The key indications for this class of drug are NSCLC and CRC, although they are being tested in numerous other settings, including glioblastoma and head and neck cancer. A great deal of effort is still going into evaluating and optimizing the use of these agents to maximize response rates and survival. However, as their routine use becomes widespread, other issues are emerging, such as acne vulgaris. Because acne vulgaris has a unique pathology, and the pathology and etiology of rash are unclear yet distinct from acne vulgaris, using such terms as _acne_, _acne-like_, or _acneiform_ should be avoided. Until there is a specific dermatological definition, rash is best described using phenotypic terms for its appearance and location. It is currently unknown which agents are best for treating rash. Clinical trials of rash treatments are urgently required, and suggestions for agents to consider are made based on current knowledge. The effect of dose reduction or interruption on rash should also be investigated. Secondarily infected rash may be more frequent than has been previously recognized, and some investigators favor empiric use of an oral antibiotic if this appears to be the case. Suggestions for patients include makeup to camouflage the rash and an emollient to prevent and alleviate skin dryness. The increasing use of HER1/EGFR-targeted agents makes managing rash important. We hope the outcomes from this Forum provide background for future studies. The Oncologist 2005;10:345–356.

<table>
<thead>
<tr>
<th>Agent (trade name)</th>
<th>Specificity</th>
<th>Type</th>
<th>Sponsor</th>
<th>Development phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib (Iressa®)</td>
<td>HER1/EGFR</td>
<td>TKI</td>
<td>AstraZeneca</td>
<td>Launched</td>
</tr>
<tr>
<td>Cetuximab (Erbitux®)</td>
<td>HER1/EGFR</td>
<td>mAb</td>
<td>Bristol-Myers Squibb</td>
<td>Launched</td>
</tr>
<tr>
<td>Erlotinib HCl (Tarceva™)</td>
<td>HER1/EGFR</td>
<td>TKI</td>
<td>Genetech Inc., OSI Pharmaceuticals Inc., F. Hoffmann-La Roche</td>
<td>Launched</td>
</tr>
<tr>
<td>Lapatinib (GW-572016)</td>
<td>HER1/EGFR, HER2</td>
<td>TKI</td>
<td>GlaxoSmithKline</td>
<td>Phase III</td>
</tr>
<tr>
<td>Panitumumab (ABX-EGF)</td>
<td>HER1/EGFR</td>
<td>mAb</td>
<td>Abgenix (Amgen)</td>
<td>Phase III</td>
</tr>
<tr>
<td>EMD 72000</td>
<td>HER1/EGFR</td>
<td>mAb</td>
<td>EMD Pharmaceuticals</td>
<td>Phase II</td>
</tr>
<tr>
<td>EKB-569</td>
<td>HER1/EGFR, HER2</td>
<td>TKI</td>
<td>Wyeth</td>
<td>Phase II</td>
</tr>
<tr>
<td>Canertinib</td>
<td>Pan HER</td>
<td>TKI</td>
<td>Pfizer</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Abbreviations: EGFR = epidermal growth factor receptor; mAb = monoclonal antibody; TKI = tyrosine-kinase inhibitor.
namely the etiology and management of the rash that is a common side effect of all HER1/EGFR-targeted agents.

HER1/EGFR inhibitor-associated rash is mostly mild to moderate, but can be more severe in some cases (Fig. 1), leading to dose reduction, dose interruption, or treatment cessation when considered intolerable by the patient or oncologist. Even when not considered severe by the prescriber, patients must find ways to cope with the chronic discomfort or itching and appearance of the rash, and also avoid repeated secondary infections. We currently know little about the etiology of this rash or how to manage it, but treatments are needed to alleviate the physical and/or emotional discomfort suffered by some patients, particularly those with advanced-stage cancer and poor prognosis. Effective rash management will also be essential if, in the future, HER1/EGFR-targeted agents are used earlier in therapy or for longer periods of time. Another consideration is the correlation reported in some studies between rash incidence/severity and clinical outcome (response and/or survival) [2, 3]. More data are required, but if this is proven, rash could be used as a surrogate marker of activity. However, using rash in this way would mean that effective management is essential.

HER1/EGFR-INHIBITOR RASH MANAGEMENT FORUM
While HER1/EGFR-targeted agents continue to be investigated and integrated into clinical practice, new areas of study have emerged. To recommend areas for research and to provide preliminary suggestions for managing rash, oncologists and dermatologists with experience with HER1/EGFR-targeted agents attended the HER1/EGFR-Inhibitor Rash Management Forum in New York City in January 2004. Table 2 shows the Forum’s objectives.

This article reports on the suggestions from this meeting and gives a brief summary of published information. However, because of the lack of trials evaluating rash therapies, evidence-based treatment recommendations are not yet possible. The suggestions are only intended to assist the future investigation of agents to manage rash and to help clinicians when making decisions regarding patient management. The suggestions are based on the unpublished knowledge of the experts at the Forum and current data on rash treatment, pathology, and etiology.
RASH: A COMMON SIDE EFFECT OF HER1/EGFR-TARGETED THERAPY

There is a high incidence of rash in patients treated with agents that inhibit HER1/EGFR. Rash occurs with tyrosine-kinase inhibitors, such as erlotinib and gefitinib, and anti-HER1/EGFR monoclonal antibodies, like cetuximab, EMD72000, and panitumumab (formerly ABX-EGF). Phase I data from dose-escalation studies show that rash is dose related [4-6]. The incidence of rash/dermatological events varies among trials and comparisons are complicated by the different terms for describing it. Common terms used to describe the HER1/EGFR-inhibitor associated rash are rash [7], acne [8, 9], acneiform skin reaction [10], acneform rash [11], acneform follicular rash [12], acne-like rash [4, 13, 14], maculopapular skin rash [15], and monomorphic pustular lesions [6].

The incidence of rash with erlotinib alone (150 mg/day) is 68% using the medDRA™ term rash not otherwise specified [7], and 75% using any medDRA™ preferred term containing rash, dermatitis, or acne [16, 17]. Dry skin is reported in 19%-35% of patients receiving erlotinib monotherapy [7, 16, 17]. The incidence of rash with gefitinib monotherapy is 43% and 54% with 250 and 500 mg/day, respectively. Acne and dry skin were categorized separately. Acne occurs in 25% and 33% of patients treated with gefitinib 250 and 500 mg/day, respectively, and dry skin in 13% and 26% [18]. Rash with cetuximab is commonly called acneform rash; it is defined as any event described as acne, rash, maculopapular rash, pustular rash, dry skin, or exfoliative dermatitis. It occurred in 88% of patients treated with cetuximab in combination with irinotecan, and in 90% of patients treated with cetuximab monotherapy [11]. In a phase II trial with panitumumab, 100% of patients had rash, although it is unclear how rash was defined [19].

Rash is generally mild (grade 1) to moderate (grade 2), and severe rash (grade 3/4) is uncommon [7, 11, 16-18]. However, the sometimes variable interpretation of the scales used to grade rash, and also the various terms used to describe it, make it difficult to compare the severity of rash between trials and agents. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) is most commonly used to grade adverse events in clinical trials with HER1/EGFR-targeted agents (Table 3). The attendees thought that the grading system may be improved if grade 2 rash were subdivided based on whether the rash interferes with the patient’s daily life, and if intervention or management is needed. A clear definition of when rash is dose limiting (grade 3 rash) and when dose...
reduction may need to be considered would also be beneficial. This could be when the patient finds the rash intolerable (either because of pain, itching, or appearance) and symptomatic management has failed. The advisors also noted that rash intensity (determined by factors like number of papules, discomfort caused, and extent of erythema) should be an important component of any grading scale; however, the absolute number of lesions in a patient, without associated physical discomfort, does not necessarily constitute a basis for a dose reduction or delay. Finally, a photo library of grade 1, 2, and 3 rashes would help clinicians to grade rash accurately. These considerations are summarized in Table 4.

Clinical experience also shows that rash commonly occurs within the first 2 weeks of treatment [4, 6, 11, 17, 20, 21], although time to first rash appearance may be related to the agent and dose [22]. There are frequent anecdotal reports of rash improving or resolving spontaneously, generally quite gradually, in spite of continued treatment [5, 6, 23]. Such frequent spontaneous improvements make it difficult to assess the usefulness of a rash treatment other than in an adequately controlled clinical trial. Other events such as pruritus, erythema, and paronychial inflammation associated with the lateral nail folds of the toes and fingers are reported frequently [9, 11, 16, 17]. Evidence suggests paronychia may occur after a longer period of treatment [24–26].

It is important to clearly define the likely occurrence and resolution of rash with different agents, so that clinicians know what to expect when using these agents, and so the incidence of rash can be compared with different agents. In addition, when guidelines are available to manage rash, clinicians need to assess and characterize rash accurately and reproducibly so that guidelines can be implemented correctly.

**Rash and Response/Survival**

Data from several clinical trials with HER1/EGFR-targeted agents show a positive correlation between rash and response and/or survival [2, 3, 27–33]. Two other trials with gefitinib also show a trend toward rash and response [13] and survival [34]. These findings suggest that rash might be a surrogate marker of efficacy. In these trials rash is assessed using NCI-CTC, so the data may be subject to the problems associated with accurately interpreting the criteria for this type of rash discussed earlier.

To find whether rash is an independent surrogate marker of activity and may be used as a tool to predict response, it is essential to analyze the correlation between grade of rash and response/survival in all trials. In addition, two studies to investigate the feasibility of dose-escalating erlotinib until a tolerable rash occurs are in progress in patients with NSCLC and glioma, respectively. Subsequently, a prospective study of dose-adjusted erlotinib would be needed to determine if rash can be used as a tool to predict response.

We also need to understand the etiology of rash fully to prove conclusively that rash can predict response.

**Etiology and Pathology**

Data on the etiology of rash are limited. It has been known for some time that HER1/EGFR is expressed in epidermal and follicular keratinocytes, sebaceous epithelium, eccrine epithelium, dendritic antigen-presenting cells, and various connective tissue cells [35, 36], so these areas are potential targets for a mechanism-based reaction. The exact role of HER1/EGFR in skin is not fully understood although it is involved in many normal epidermal processes [36], and abnormal expression is implicated in epithelial tumor formation [37] and epidermal hyperproliferation disorders such as psoriasis [38].

Preclinical studies predicted a cutaneous effect of HER1/EGFR inhibitor use. Mice with a HER1/EGFR dominant negative mutation have curled whiskers and short hair that becomes progressively sparse. Their hair follicles eventually disappear, accompanied by a macrophage- and multinucleated giant cell-driven inflammatory reaction, and interfollicular epidermal hyperplasia [39]. Mice treated with erlotinib have frequent subcorneal pustules (containing a neutrophilic influx) and inflammation that is usually superficial, but can occasionally involve hair follicles [40]. Despite these studies, animal models provide few clues about the etiology of the rash in humans.

Busam et al. presented the largest study of rash to date [24]. After histological analysis of rash samples from 10 patients receiving cetuximab, they concluded that this rash is characterized by a lymphocytic perifolliculitis or suppurrative superficial folliculitis, but has no infectious etiology. They hypothesized that suppurative inflammation occurs in response to follicular rupture. The perifollicular inflammation was more difficult to explain because the follicle is intact; they proposed that it could occur in response to a change in the cutaneous microflora arising from altered follicular growth and differentiation. Several studies also...
report cases of folliculitis with erlotinib, gefitinib, and cetuximab, several noting neutrophilic involvement or other chronic inflammatory changes [6, 20, 41–43]. In one report, more advanced lesions were associated with destruction of the follicle with perifollicular granuloma formation, dermal edema, and vasodilation [20]. Although some studies state that rash is sterile [20, 41], others report that microorganisms are present, particularly associated with follicular plugs [24, 42, 43]. Interestingly, several studies show that, unlike acne vulgaris the sebaceous glands are not affected [20, 43, 44]. The stratum corneum of the epidermis is also reported to be thinner, more compact, and without the basket-weave pattern in the skin of patients treated with cetuximab or gefitinib [20, 43, 44].

The histological findings show that, in agreement with clinical observations, the rash has a strong inflammatory element. More studies are required to define the exact histology of the rash (so, clarifying the differences from acne vulgaris), key structures involved, primary cellular mediators, and extent/incidence of secondary infection. In addition, we need to address why rash occurs in specific regions, what determines severity, and why both the location and severity can alter during treatment. Finally, as we have little knowledge of why HER1/EGFR inhibitors can cause inflammatory rash, studies to clarify the relationship between rash etiology and HER1/EGFR inhibition are urgently required. Table 5 shows suggestions for investigating rash etiology.

Is HER1/EGFR Inhibitor-Associated Rash Like Acne Vulgaris?

In reports of studies of HER1/EGFR-targeted agents, the terms acne, acne-like, acneiform, or acneform are frequently used to describe rash. This is presumably because the pustular, inflammatory appearance and facial location of the rash may resemble acne vulgaris, especially to non-dermatologists. However, these terms imply that the rash has some pathological and etiological characteristics in common with acne vulgaris.

Acne vulgaris is characterized clinically by both noninflammatory lesions known as comedones (blackheads and whiteheads) as well as inflammatory papules, pustules, and nodules. The rash associated with HER1/EGFR-targeted agents is dominated by pustules that develop an impetiginous honey-combed crust in serious cases. Noninflammatory comedones have not been described. The histopathology of acne vulgaris is characterized by a preclinical stage known as the microcomedo, which is a sebaceous follicle distended by large clumps of abnormally desquamated follicular corneocytes. This precursor stage is not clinically visible and can evolve along two pathways. With increased accumulation of abnormally desquamated corneocytes, sebaceous follicles become distended and clinically visible as noninflammatory comedones. Papules and pustules develop with the influx of neutrophils and lymphocytes. Overgrowth of Propionibacterium acnes causes the inflammatory phase through a variety of mechanisms.

In rash associated with HER1/EGFR-targeted agents, microcomedones and comedones are not seen. Pustules show an intrafollicular collection of neutrophils—the hallmarks of an infectious folliculitis.

These findings clearly indicate that this rash is not acne vulgaris and does not appear to have acne-like pathology/etiology. Hence, it is not surprising that acne medications do not, thus far, seem to be effective and could exacerbate the rash. Therefore, rash medication should not be prescribed on the basis that the rash is like acne vulgaris.

Describing Rash Accurately

Because the etiology and pathology of rash are unclear and require further investigation, we should not describe it in terms that imply a certain pathology or etiology, rather we should use phenotypic terms relating to its appearance and location. Recommended terms are pustular/popular rash, pustular eruption, or follicular and intrafollicular pustular eruption. In the future, it is likely that improved understanding of rash will enable us to name it based on its pathology and etiology. Preliminary data indicate that it is a new dermatological entity, but more studies are required to confirm this.

Managing Patients with Rash

At the time of this meeting there have been no controlled clinical trials of agents for treating the rash associated with HER1/EGFR inhibitors, so we cannot make
evidence-based recommendations for rash management. A key recommendation from the Forum was for investigators to begin carefully controlled efficacy trials of agents to treat rash. To help clinicians we used available information, knowledge of rash’s inflammatory nature, and the unpublished experience of the oncologists and dermatologists at the Forum to develop broad suggestions to assist when a patient presents with rash and when designing trials to investigate agents for rash management. As more HER1/EGFR-targeted agents are licensed and their use becomes more widespread, evidence-based guidelines for rash management will be essential.

**Diagnosing HER1/EGFR Inhibitor-Associated Rash and When to Refer to a Dermatologist**

HER1/EGFR inhibitor-associated rash has a characteristic pustular/papular appearance, and usually involves the face, head, and upper torso. Patients should be referred to a dermatologist if lesions have an uncharacteristic appearance or distribution, or if there is necrosis, blistering, or petechial/purpuric lesions. Patients treated with HER1/EGFR-targeted agents may occasionally suffer other dermatological conditions. Pruritus, dry skin, and erythema are relatively common and expected, but unrelated complications (e.g., simplex and herpes zoster) may occur. These are rare and appear unrelated to rash. The expected incidence is hard to quantify accurately as patients with dermatological conditions are excluded from clinical trials with HER1/EGFR-targeted agents. Patients with atypical manifestations should be referred to a dermatologist.

Inflammatory-based pustules should be sterile, but experience among the group shows that secondary infections are more common than previously described. Some organisms (e.g., *Staphylococcus aureus*) produce a classic impetigo appearance, indicated by a yellowish/brown crust overlying inflammatory lesions, significant oozing of fluid from lesions, or an abrupt change in the appearance of lesions (particularly if they differ from those in other areas). Cellulitis typically presents with a localized area of warmth, erythema, and tenderness, and can be associated with fever. The most common presentation is recognized only by an increase in pustules. However, the signs of secondary infection can be subtle, especially in patients who are neutropenic or taking systemic steroids. The best way to identify secondarily infected rash is to inspect the rash regularly. Culturing the pustules or crusting can be considered if the rash worsens.

Patients taking steroids for their cancer may suffer steroid-induced acne. This may result in its being confused with HER1/EGFR inhibitor-associated rash because of its pustular nature. Steroid-induced acne is a monomorphous eruption with widespread 2–3-mm firm, erythematous papules primarily on the trunk. It is differentiated from rash because the papules are firm to the touch and any attempt to open and culture will not reveal any purulent material. Inflammatory-based pustules should be sterile, but experience among the group shows that secondary infections are more common than previously described. Some organisms (e.g., *Staphylococcus aureus*) produce a classic impetigo appearance, indicated by a yellowish/brown crust overlying inflammatory lesions, significant oozing of fluid from lesions, or an abrupt change in the appearance of lesions (particularly if they differ from those in other areas). Cellulitis typically presents with a localized area of warmth, erythema, and tenderness, and can be associated with fever. The most common presentation is recognized only by an increase in pustules. However, the signs of secondary infection can be subtle, especially in patients who are neutropenic or taking systemic steroids. The best way to identify secondarily infected rash is to inspect the rash regularly. Culturing the pustules or crusting can be considered if the rash worsens.

**Advice for Patients**

The group developed suggestions for patients to help them camouflage the rash, make it look less severe, and/or alleviate discomfort (Table 7). Patients can be advised the rash can be covered with makeup, and this should not make it worse. A dermatologist-approved cover-up (e.g., Dermablend®) can be used although any type of foundation may be useful. The makeup should be removed with a hypoallergenic (skin-friendly) liquid cleanser (e.g., Neutrogena®, Dove®, or Ivory Skin Cleansing Liqui-Gel®). All patients should be strongly encouraged to use emollients (e.g., Neutrogena Norwegian Formula Hand Cream® or Vaseline Intensive Care Advanced Healing Lotion®) to prevent and alleviate the skin dryness. If the rash is aggravated by sunlight, patients should use a good sunscreen like Anti Helios® sunscreen. Finally, we suggest that patients are advised not to use over-the-counter acne medications (e.g., benzoyl peroxide), as these treatments could make it worse.

**Analgesia**

Some patients report that HER1/EGFR inhibitor-associated rash is painful. This is particularly common in patients with

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**Table 6. Considerations for diagnosing HER1/EGFR inhibitor-associated rash and when to refer to a dermatologist**

<table>
<thead>
<tr>
<th>Typical rash presentation:</th>
<th>Considerations for diagnosing HER1/EGFR inhibitor-associated rash and when to refer to a dermatologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>pustular/papular appearance</td>
<td>pustules primarily on the trunk</td>
</tr>
<tr>
<td>usually involving the face,</td>
<td>papules are firm to the touch and any attempt to open and culture will not reveal any purulent</td>
</tr>
<tr>
<td>head, and upper torso</td>
<td>material</td>
</tr>
<tr>
<td>often accompanied by pruritus, dry skin, and erythema</td>
<td>less erythema than HER1/EGFR-associated rash</td>
</tr>
</tbody>
</table>

**Characteristics of secondary infection:**

- yellowish/brown crust overlying inflammatory lesions
- significant oozing of fluid from lesions
- and/or an abrupt change in the appearance of lesions (particularly if lesions differ from those in other areas)

**Differentiating characteristics of steroid-induced acne:**

- monomorphous eruption with widespread 2–3-mm firm, erythematous papules primarily on the trunk
- papules are firm to the touch and any attempt to open and culture will not reveal any purulent material
- less erythema than HER1/EGFR-associated rash

**Refer the patient to a dermatologist when:**

- lesions have an uncharacteristic appearance or distribution
- there is necrosis, blistering, or petechial/purpuric lesions
- patients have atypical dermatological manifestations unrelated to rash
Table 7. Suggestions for patients with rash

<table>
<thead>
<tr>
<th>Makeup</th>
<th>Moisturizer</th>
<th>Sunlight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash can be covered with makeup; this should not make it worse (use a dermatologist-approved cover-up, e.g., Dermablend®, or any other type of foundation)</td>
<td>Use emollients to prevent and alleviate the skin dryness, e.g., Neutrogena®, Dove®, or Ivory Skin Cleansing Liqui-Gel®</td>
<td>If the rash is aggravated by sunlight, use a good sunscreen, e.g., Anti Helios®</td>
</tr>
<tr>
<td>Remove makeup with a skin-friendly liquid cleanser, e.g., Neutrogena®, Dove®, or Ivory Skin Cleansing Liqui-Gel®</td>
<td>Use emollients to prevent and alleviate the skin dryness, e.g., Neutrogena Norwegian Formula Hand Cream® or Vaseline Intensive Care Advanced Healing Lotion®</td>
<td>Use emollients to prevent and alleviate the skin dryness, e.g., Neutrogena Norwegian Formula Hand Cream® or Vaseline Intensive Care Advanced Healing Lotion®</td>
</tr>
<tr>
<td>Over-the-counter acne vulgaris medications (e.g., benzoyl peroxide) are not advised; this rash is not like acne vulgaris and these treatments could make it worse</td>
<td>Over-the-counter medications</td>
<td>If the rash is aggravated by sunlight, use a good sunscreen, e.g., Anti Helios®</td>
</tr>
</tbody>
</table>

rash that is accompanied by erythema/inflammation. If the rash is painful, consider prescribing standard analgesia before trying other management options. If the pain is localized or becomes more severe, then cellulitis should be considered.

Evaluating Agents to Treat Rash

Potential agents for rash management fall into two categories: A) agents based on etiology, and B) symptomatic, empirical, nonvalidated therapies. As discussed previously, our understanding of rash etiology is limited, preventing the identification of agents for investigation based on etiology. However, we hope our knowledge will improve and novel routes of investigation established. For example, agents that reverse HER1/EGFR inhibition in the skin, block damaging cytokine cascades, or treat secondary infections based on the identification of exact bacterial etiology may be considered in the future.

Currently, agents have been selected for investigation based on symptoms. Because there are no controlled trials, the efficacy of all the agents is unproven. There are anecdotal reports of treatments, such as topical and systemic antibiotics, topical and systemic corticosteroids, retinoids, and antihistamines [5, 20, 24, 41, 45-47], and one preliminary report from an uncontrolled trial of alpha-hydroxy acids with or without gentamicin and betamethasone [48]. While it is encouraging that rash treatment is being investigated, the lack of a control, especially since rash resolves spontaneously in many patients, means the effectiveness of this combination remains unclear and its use in the clinic cannot be recommended at this time. Dose reduction or interruption is commonly used in clinical trials of oral HER1/EGFR inhibitors to manage adverse events. In the phase III trial of erlotinib 150 mg/day in patients with advanced NSCLC following chemotherapy, dose reductions in increments of 50 mg (to a minimum of 50 mg/day) were permitted for hematologic and other toxicities not controlled by optimal supportive care or not tolerated by the patient. In this trial, 6% of erlotinib-treated patients had dose reductions because of grade 3/4 rash, and only 1% of patients withdrew as a result of grade 3/4 rash or diarrhea. The findings from this large phase III trial suggest that adjusting the dose of erlotinib is a useful approach for managing severe rash with this agent [21, 49].

A key recommendation was for investigators to begin carefully controlled efficacy trials of agents to treat rash. As the normal course of rash is to wax and wane, well-controlled trials are necessary to determine the efficacy of marginally effective therapies. An important step toward identifying effective agents is to find out if animal models could be used to test therapies, or at least narrow options before beginning clinical trials. We hope new data will enable us to identify potentially active agents based on rash etiology. To assist the evaluation of agents to treat rash, we encourage investigators to photograph rash so there is a lasting record of the effect of treatment.

Trial Design

To test the effectiveness of topical agents, we recommend that investigators design trials where one side of the face/body is treated for a week (consider using an emollient on the other side). If the agent is effective, continue treatment on the whole face/body. Topical agents could be ineffective because they may not penetrate the skin deep enough. However, they may be useful before a severe rash appears. Finally, secondary infection is an important consideration. More frequent culturing of pustules will enable us to assess the extent of secondary infection, the type of colonizing bacteria, and treatments.

Agents for Consideration

Based on our albeit limited knowledge of rash pathology and etiology, and anecdotal reports of agents used to manage rash, agents that have or could be considered for rash management were discussed (Table 8).

Topical Corticosteroids

The experience of the attendees suggests that topical corticosteroids are largely ineffective in patients with advanced/severe rash. However, one hypothesis is that they may have some efficacy if used early in therapy (in patients with mild rash), or after antibiotics, to combat inflammation and prevent infection. So far, there have been no clinical trials to test this hypothesis. If this hypothesis were investigated in a...
Table 8. Agents for consideration

<table>
<thead>
<tr>
<th>Primary Rash</th>
<th>Topical corticosteroids</th>
</tr>
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<tr>
<td>Data suggest they are ineffective, but consider investigating high-potency agents, e.g., clobetasol propionate (Temovate®) early in therapy in patients with mild rash; can be used on the face</td>
<td></td>
</tr>
</tbody>
</table>

Analgesia
Consider before reducing the dose of the HER1/EGFR-targeted agent

Systemic immunomodulatory agents
No data to support use. Consider evaluating a short course in patients with severe rash that is causing physical discomfort

Topical immunomodulatory agents
Warrant investigation

Retinoids
No data to support use. Use is not advised, as their skin-drying effects may exacerbate rash

Other acne medications
Should not be prescribed on the basis that the rash is acne like Benzoyl peroxide will aggravate dry skin and should not be used Preliminary data indicate alpha-hydroxy acids should be evaluated

Pruritus
Consider investigating an antihistamine, such as diphenhydramine (Benadryl®), or hydroxyzine hydrochloride (Atarax®)

Secondarily Infected Rash
Prevention
Consider intranasal mupirocin (Bactroban Nasal®)
Treatment (based on empirical, nonvalidated data)
Short course of oral antibiotics; consider tetracyclines like minocycline (Minocin®) because of their proposed weak anti-inflammatory effects and reasonably good activity against S. aureus
If S. aureus infection is confirmed, or a clinical diagnosis of impetigo, consider topical mupirocin (Bactroban®)
Consider a clinical trial to investigate topical antibiotics e.g. topical clindamycin (Cleocin®, Clindaderm®)

Pustule culture
If antibiotic resistance is suspected, culture to determine the bacterial strain and then treat

no data from clinical trials to support this approach or confirm that such an approach would not interfere with the therapeutic efficacy of the HER1/EGFR inhibitor. Therefore, such an approach cannot be recommended for routine clinical use. Before investigating longer-term or the more general use of systemic immunomodulation, the effect on HER1/EGFR inhibition in the tumor needs to be established.

Topical Immunomodulatory Agents
Studying topical immunomodulatory agents (such as pimecrolimus [Elidel®]) would be of interest, and, considering the inflammatory nature of the rash, warrants clinical investigation. However, we currently have no clinical data on which of these agents to recommend except in a clinical trial. A phase II trial of Elidel® in patients with HER1/EGFR tyrosine kinase inhibitor-associated rash will start soon.

Both in clinical trials or practice, if one chooses to try these agents, we recommended that one side of the face and/or body only should be initially treated to see if the treatment is effective, ineffective, or worsens the rash. Until/unless effectiveness is demonstrated and documented in this manner, it is impossible to establish if the patient should continue the topical treatment, since the rash can improve and worsen spontaneously. It is noteworthy that at the time of writing, none of the authors have demonstrated clinical benefit with any topical therapy when evaluated in this manner, i.e., we have yet to see a patient in whom treating one side with a topical therapy substantially improved the rash on that side compared with the other.

Retinoids
The attendees suggest that topical retinoids should be avoided, as their skin-drying effects are likely to exacerbate rash. To date, there are no data to suggest that topical retinoids are beneficial in this setting.

Other Acne Medications
Because the pathologies of acne vulgaris and HER1/EGFR inhibitor-associated rash are different, acne-specific medications should not be prescribed because the rash appears to be like acne vulgaris. For example, benzoyl peroxide should not be used, as this will aggravate dry skin. Alpha-hydroxy acids have been investigated in patients with grade 1 rash in a clinical trial [48]. Because the trial was uncontrolled, it is unclear whether the improvement noted was a result of the treatment or just the natural course of rash.

Antipruritic Therapy
Patients often find pruritus a disturbing, chronic symptom and unfortunately there is no effective treatment. Antihistamines, such as diphenhydramine (Benadryl®) or hydroxyzine
Secondarily Infected Rash

As discussed, secondary infection appears to be more common than previously thought and can make the rash worse, particularly in appearance. To reduce the likelihood of secondary infection, consider intranasal mupirocin (Bactroban Nasal®) applied once daily to each nostril. Secondarily infected rash should be treated with a short course of oral antibiotics; consider tetracyclines such as minocycline (Minocin®) because of their proposed weak anti-inflammatory effects and reasonably good activity against S. aureus, although many different antibiotics may be effective. Although some weak anecdotal evidence suggests that topical antibiotics may be effective, e.g., topical clindamycin (Cleocin®, Clindaderm®), there have not been any clinical trials, and no cases showing clear benefit. Topical antibiotics should be evaluated in a controlled clinical trial, considering the design recommendations discussed previously. If antibiotic resistance is suspected, culture the pustules to determine the bacterial strain before treating. If there is a clinical diagnosis of impetigo, or if secondary infection with S. aureus is confirmed, consider topical mupirocin (Bactroban®) (Table 8).

If agents are used outside a trial setting, their effectiveness should be evaluated after 1 week, and treatment continued for another week. If there is no improvement after 2 weeks, the treatment should be considered ineffective, and discontinued.

Future Direction

During the HER1/EGFR Inhibitor Rash Management Forum it became clear how little we know about this common side effect. The process of education begins by sharing our limited knowledge of this rash with others treating these patients. This ensures that patients receive the best possible advice and treatment for this sometimes distressing side effect in what are often the final months of their lives. The next stage is to educate ourselves further so we can understand the cause of this rash, and provide effective, evidence-based treatment recommendations. Conducting well-controlled clinical trial to evaluate agents is essential if we are to achieve this goal. Finally, we need to establish whether rash can improve the efficacy of these agents. If it can, it will be a powerful tool in ensuring that they have maximum benefit. It will also bring the challenge of preventing rash from becoming dose limiting. Developing ways to manage rash effectively is vital if we are to meet this challenge.

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Potential Conflicts of Interest

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