Management of Skin Toxicities of Anti-EGFR Agents in Patients with Pancreatic Cancer and Other GI Tumors by Using Electronic Communication: Effective and Convenient

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Summary

Erlotinib has been FDA approved to be used in combination with gemcitabine as the first line treatment in advanced pancreatic cancer patients. Skin rash has been documented as one of the commonest adverse reactions in patients receiving erlotinib and other EGFR inhibitors. Draw back to this reaction leads to: 1) drug discontinuation or dose reduction; 2) impairs quality of life; and 3) Puts patients at risk of superinfection. Monitoring patients closely and initiating immediate skin care is recommended. However, patients forget how the rash started and when. No standard treatments exist secondary to the diversity of symptoms, variability and intermittent occurrence in relation to the cancer therapy. In addition, there is slow improvement with medical treatment. Also, patients need to make extra visits to doctor’s office for skin management when in needed in addition to chemotherapy appointments. Late presentation for medical attention leading to complications, such as sepsis. We here experience a novel way of assessing and managing the skin rash using the electronic media. We suggest that electronic communication is of crucial importance to detect early, diagnose and treat anti-EGFR related skin rash in order to continue the benefit of anti-EGFR.

Introduction

- Erlotinib has been FDA approved to be used in combination with gemcitabine as the first line treatment in advanced pancreatic cancer patients [1].
- Skin rash has been documented as one of the commonest adverse reactions in patients receiving erlotinib and other EGFR inhibitors.
- Draw back to this reaction leads to:
  1. Drug discontinuation or dose reduction,
  2. Impairs quality of life, and
  3. Puts patients at risk of superinfection [1]
- Monitoring patients closely and initiating immediate skin care based on general guidelines is highly recommended.

Secondary adverse reactions seen with anti-EGFR therapy include xerosis, pruritus, paronychia, hair abnormality, and mucositis [2].

A phase III randomized controlled trial by National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) has shown a statistically significant survival benefit of gemcitabine plus erlotinib compared with gemcitabine alone. The combined treatment arm demonstrated an 18% reduction in the risk of death or an overall 22% improvement in survival than the gemcitabine alone arm, and it was statistically superior in 1-year survival (23.8% vs. 19.4%; P=0.028) and in median survival (6.4 vs. 6.0 months) [3].

The rash develops as early as three days after commencement of erlotinib therapy, with median onset of eight days [4].

Erlotinib, a small-molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor has been approved by FDA for patients with pancreatic cancer and non-small cell lung cancer [1].

Skin toxicity may lead to drug discontinuation or dose reduction, impair patients’ activities and exposes the skin to bacterial infections. Preservation of quality of life in these patients is crucial [1].

Toxicity is seen in at least 79% patients treated with erlotinib [5].

Grade 3-4 rash was documented in 9% of erlotinib treated patients, requiring dose reduction in 6% and discontinuation in 1% of patients [6].
Key point: skin rash can be managed with appropriate intervention.

Skin rash occurred in 71% (grade 1-2: 66%; grade 3: 3%; grade 4: 2%); median time of onset was 10 days (range: 1-44 days) [9].

Pathogenesis of Cutaneous Toxicities

- Unknown mechanism
- Proposed pathogenesis: antibodies against EGFR in the epidermis, sebaceous glands, and hair follicles
- Inflammatory response leading to folliculitis and perifolliculitis, decreasing keratinocyte maturation and proliferation. There is a diffuse neutrophilic infiltrate in the dermis. This results in an acneiform rash and dry skin

Characteristics of Cutaneous Toxicities

<table>
<thead>
<tr>
<th>Grade</th>
<th>Rash characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Macular or papular eruption or erythema without associated symptoms</td>
</tr>
<tr>
<td>2</td>
<td>Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering less than 50% of body surface area</td>
</tr>
<tr>
<td>3</td>
<td>Severe, generalized erythema or papular, papulovesicular eruption, desquamation covering more than 50% of body surface area</td>
</tr>
<tr>
<td>4</td>
<td>Generalized exfoliation, ulceration, or bullous dermatitis</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

Clinical Grades of Erlotinib-Induced Rash [12]

Toxicity Description

- Mild: Generally localized papulopustular reaction that is minimally symptomatic, with no sign of superinfection and no impact on daily activities
- Moderate: Generalized papulopustular reaction, accompanied by mild pruritus or tenderness, with minimal impact upon daily activities and no sign of superinfection
- Severe: Generalized papulopustular reaction, accompanied by severe pruritus or tenderness, that has a significant impact upon daily activity and has the potential for or has become superinfected

Grading Rash: A Potential Algorithm [13]

- Mild
  - Generally localized
  - Minimally symptomatic
  - No impact on activities of daily living
  - No sign of superinfection
- Moderate
  - Generalized
  - Mild symptoms (e.g., pruritus, tenderness)
  - Minimal impact on activities of daily living
  - No sign of superinfection
- Severe
  - Generalized
  - Severe symptoms (e.g., pruritus, tenderness)
  - Significant impact on activities of daily living
  - Potential for superinfection

This slide shows mild, moderate, and severe rash in patients treated with erlotinib. This grading system should not be construed as per Genentech, Inc. (South San Francisco, CA, USA) or OSI Pharmaceuticals, Inc. (Long Island, NY, USA) recommendations [13, 14]. It was developed by medical advisors at the “Skin Toxicity Forum” held in Chicago, Illinois, during October 2006 [13]. These medical advisors were paid by Genentech, Inc., OSI Pharmaceuticals, Inc., and F.
Hoffmann-La Roche AG (Basel, Switzerland), to participate in the forum. Other medical experts may have a different approach to managing rash. Rash typically appears on the face and/or upper body in varying degrees and tolerability. For some, severe rash was tolerable; for others, mild rash was intolerable. The rash associated with erlotinib treatment is not acne, though its appearance is similar to acne. Rash varies in presentation and degree. An interactive discussion regarding grading is encouraged to demonstrate the subjective nature of EGFR rash grading currently used in clinical practice.

**General Principles in Management**

- Important to treat rash in order to continue treatment
- No standard treatments or guidelines
- Skin care and hygiene: Avoid sunbathing, direct sunlight, hot bath or humidity
- Makeup coverage of rash is not contraindicated and should be removed with hypoallergenic liquid cleansers
- Emollients to prevent xerosis

**Management [15]**

- Topical antibiotics if pustules are present or about to develop
- Topical steroids: controversial with secondary side effects
- No clinical data for topical immunomodulatory agents
- Topical retinoids are used for follicular eruptions but not recommended secondary to skin dryness and peeling [16]
- Aztec medications are not as effective as steroids/antibiotics [17]
- Systemic: For severe grade 3-4 lesions
  - Steroids: No data with concern of interaction with anti-EGFR [8]
  - Antibiotics: Tetracycline plays an anti-inflammatory role [18]

**Nonpharmacologic Interventions**

- Employ a proactive approach in managing skin reactions
- Suggest patients use:
  - Thick, alcohol-free emollient cream on dry area
  - Sunscreen of sun protection factor (SPF) 15 or higher, preferably containing zinc oxide or titanium dioxide
- If patient presents with a rash:
  - Verify appropriate administration
  - Erlotinib should be taken at least 1 hour before or 2 hours after the ingestion of food
  - Treat per the provided potential treatment algorithms or your institution’s guidelines

**Proposed Management** [12]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Erlotinib</th>
<th>Treatment</th>
<th>Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Continue erlotinib at current dose and monitor for change in severity</td>
<td>Topical hydrocortisone 1% or 2.5% cream and/or cetirizine 1% gel</td>
<td>Re-examine in 2 weeks; if no improvement, treat as moderate grade</td>
</tr>
<tr>
<td>Moderate</td>
<td>Continue erlotinib at current dose and monitor for change in severity; continue treatment of rash</td>
<td>Hydrocortisone 2.5% cream or cetirizine 1% gel or tranexamic acid 5% cream plus desquame 100 mg bid or minocycline 100 mg bid</td>
<td>Re-examine in 2 weeks; if no improvement, treat as severe grade</td>
</tr>
<tr>
<td>Severe</td>
<td>Reduce erlotinib dose per drop intake and monitor for change in severity; continue treatment of rash</td>
<td>Treat as above to moderate grade, and may consider adding methylprednisolone dosing pack</td>
<td>Re-examine in 2 weeks if no response, consider dose interruption or discontinuation</td>
</tr>
</tbody>
</table>

**Key points:**
- Skin rash can be managed with appropriate intervention;
- Erlotinib should be taken at least one hour before or two hours after the ingestion of food.

**Rash Assessment and Management Algorithm** [13]

Key point: erlotinib should be taken at least one hour before or two hours after the ingestion of food. This slide is designed to open a dialogue among attendees on how they manage rash in their practice. Measures: they take upfront, such as patient education initiatives and prophylactic measures, should be discussed. Management options, once a patient develops a rash while on erlotinib, should be discussed as well.

- Do they dose reduce erlotinib? Why?
- Do they discontinue erlotinib?
- Do they modify the erlotinib regimen?
- Do they maintain erlotinib at the current dose and treat the rash, and if so, how?

**Pre-Emptive Skin Toxicity Treatment With Panitumumab for CRC (STEPD)** [19]

- Skin therapy consisting of:
  - Moisturizers
  - Sunscreen (PA+++, SPI > 15, UVA/UVB protection)
  - Topical 1% hydrocortisone cream
  - Doxycycline 100 mg bid
  - 95 patients randomized to pre-emptive (24 h prior to 1st dose) or reactive (after skin toxicity developed)

**6-week evaluation**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Pre-emptive</th>
<th>Reactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2.9% (1.35%)</td>
<td>4.0% (7.54%)</td>
</tr>
<tr>
<td>3</td>
<td>6.0% (1.35%)</td>
<td>21.6% (10.3%)</td>
</tr>
</tbody>
</table>

**[References]**
Nimotuzumab, a humanized murine mAb created in Cuba, has demonstrated antitumor activity similar to that of other anti-EGFR mAbs and shows promise as a single agent and as an adjunct to radiation in Phase I and II clinical trials. Surprisingly, the typical severe dermatological toxicities thus far associated with anti-EGFR therapy have not been described with nimotuzumab [21].

Cetuximab, erlotinib, and gefitinib have been approved for patients with colorectal and non-small cell lung cancer refractory or intolerant to chemotherapy. The most commonly encountered adverse effect was a mild skin toxicity characterized by a sterile follicular and pustular rash that may be treated empirically and usually does not require treatment modification. Although the precise mechanism for development of rash is not well defined, it is related to inhibition of EGFR-signaling pathways in the skin, and may serve as visible markers of anti-tumor activity and therapeutic efficacy [2].

**EGFR Targeted Agents [7]**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Indications</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>MoAb</td>
<td>Locally advanced or metastatic HNSCC after initial or second line chemotherapy</td>
<td>400 mg/m² every 7 weeks followed by 250 mg/m² every 2 weeks</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>TKI</td>
<td>Locally advanced or metastatic colorectal cancer patients receiving oxaliplatin or fluoropyrimidines</td>
<td>150 mg orally daily</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>TKI</td>
<td>Non-squamous NSCLC patients who have progressed or are intolerant to platinum-based chemotherapy</td>
<td>250 mg orally daily</td>
</tr>
<tr>
<td>Nimotuzumab</td>
<td>MoAb</td>
<td>Metastatic colorectal cancer that has progressed on prior EGFR therapy</td>
<td>200 mg/m² every 2 weeks</td>
</tr>
</tbody>
</table>

**Impact of Rash on Outcome**

- **Patients forget the rash started and when**
- **No standard treatments secondary to the diversity of symptoms, variability and intermittent occurrence in relation to the cancer therapy**
- **Infrequent involvement of dermatologists**
- **No data in the literature for topical applications**
- **Slow improvement with medical treatment**
- **Access to healthcare provider**
- **Late presentation for medical attention leading to complications**

Electronic Communication: A Novel Idea

- Providing quality healthcare depends on the clinician’s ability to adequately communicate
- Written and verbal (face-to-face and telephone) communications have traditionally been the primary mechanisms
- The use of e-mail allows for follow-up, patient care and clarification of advice provided
- Inexpensive mechanism for communication

- Allows written follow-up instructions, test results and dissemination of educational materials for patients, as well as, a means for patients to easily reach their physician
- Issues of privacy, confidentiality and security must be addressed to ensure the efficacy and effectiveness

New communication technologies must never replace the crucial interpersonal contacts that are the very basis of the patient-physician relationship. Rather, electronic mail and other forms of Internet communication should be used to enhance such contacts.
Case #1
A 67-year-old white female treated with gemcitabine and erlotinib called the nurse with new development of nail infection. Patient was advised to come and see us. Due to transport, she could not come. Therefore, she was requested to take a picture with her cell phone and e-mail us.

Case #1: How Was the Patient Managed?

- Based on the picture, diagnosis of paronychia was made
- Patient was directed to stop erlotinib, and oral minocycline was started
- Patient called back after three days and told about dramatic improvement

Case #2
A Caucasian 54-year-old male with gallbladder cancer was treated with erlotinib. Patient was living in Florida and one day called my office with rash on the face. Patient e-mailed the nurse few pictures of the rash that led to its proper grading and management.

Case #3
A 56-year-old white female with pancreatic adenocarcinoma stated erlotinib at 100 mg daily. The patient returned in clinic with a papulopapular-erythematous rash on face, arms, hands, trunk, and extremities on face (Figure). The rash was pruritic and associated with dysesthesias and tenderness. The scalp, arms, and lower body were uninvolved. Ultimyacin 250 mg and oral minocycline at 100 mg daily were given for treating the rash. Meanwhile, erlotinib dose was reduced to 75 mg every other day, however, the rash continued to get worse despite of dose reduction of erlotinib. Therefore, erlotinib was temporarily discontinued after a total of 13 days of use.

A week after discontinuation of erlotinib, the patient developed pruritus with similar. The temperature is only 36.8°C, with heart rate of 114/min, and respiration rate of 30/min. Clinically, the rash highly suggestive for paronychia infection. A specimen blood and minocycline hydrochloride with total white cell count of 12,700/μL (reference range: 4000-10,000/μL) with neutrophils of 77% (reference range: 50-70%). Biopsy was performed from peripheral line and double-lobed port-a-cath. The patient was admitted to hospital and treated with intravenous antibiotics for broad-spectrum with vancomycin and Zosyn® (F. Hoffmann-La Roche Ltd). Pseudomonas and Staphylococcus infection, then treated to encompass after 3 out of 6 bottle gram-positive and gram-negative resistant. The patient was discharged. The port-a-cath was removed during hospitalization, and temporary peripherally inserted central catheter line was inserted for chemotherapy administration. Vena-cava ligature was done to control the groin-positive flow of 3 mmeters, consistent with skin flap. She was implanted with transcatheter pacing system for a total of 10 days. Topical peripheral nerve blocks and culture from the scalp started appropriately for meth young resident on the second day and five days were all negative. Her skin rash gradually improved after the discontinuation of erlotinib, and eventually disappeared after two weeks of skin care with topical minocycline gel.

Case #4
This is a Caucasian 64-year-old female with pancreatic cancer who was receiving erlotinib and cetuximab after failing gemcitabine. She called for a possibility of a grave nail-like problem. She sent us a picture. Diagnosis of paronychia was made and patient was referred to a podiatrist as well as started on “per arom” minocycline. She recovered with in 10-12 days.
Conflict of interest The authors have no potential conflicts of interest.

References


