MULTIMEDIA ARTICLE - Slide Show

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.

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].

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Key words cetuximab; Drug Therapy; Epidermal Growth Factor; erlotinib; Pancreatic Neoplasms; panitumumab; Protein Kinase Inhibitors; Receptor, Epidermal Growth Factor

Abbreviations EGFR: Epidermal Growth Factor Receptor, NCI-CTCAE: National Cancer Institute: Common Terminology Criteria for Adverse Events; FDA: Food and Drug Administration

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Skin Cutaneous Toxicities: Overview

- PA3 trial: rash was among the most common side effects reported [7].
- Typically, rash develops about 8–10 days after start of treatment [7].
- Poor performance status was inversely correlated to skin toxicity incidence. Response rate was higher in patients with at least 50% of body surface area with skin toxicity [7].
- In general, rash may appear between 1 and 113 days [7].
- Erlotinib-related rash was generally mild to moderate and is generally manageable [8].
- Occurrence of rash may be intermittent [8].
- Although rash is commonly referred to as "toxic epidermal necrolysis," it is not acute and should not be treated as acute [8].

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].

Dermatologic reactions from anti-EGFR agents, which include antibodies against the extracellular ligand-binding domain of the receptor and small molecules that inhibit activation of the EGFR-tyrosine kinase, are commonly found in sites where EGFR is expressed, such as the basal epidermal keratinocytes of the epidermis, sebaceous glands, and hair follicles. Histopathological findings of the skin lesion reveal folliculitis and perifolliculitis with a diffuse neutrophilic infiltrate in the dermis. It has been speculated that cutaneous toxicity from anti-EGFR therapy may be a result of an inflammatory response secondary to EGFR inhibition and/or decreased keratinocyte proliferation/maturation. Markers in the epidermal growth factor receptor pathway and skin toxicity during erlotinib treatment [10].

Pathogenesis of Cutaneous Toxicities

- Unknown mechanism
- Proposed pathogenetic antibodies against EGFR in the epithelium, 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

Clinical Grades of Erlotinib-Induced Rash [12]

**Toxicity Description**

- **Mild**: Generally localized papulopustular reaction, associated with minimal symptoms 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 superinfection.

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
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, high heat 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 pusules 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]
- Acne medications are not as effective as steroids/antibiotics [17]
- Systemic: For severe 3-4 lesions
  - Steroids: No data with concern of interaction with anti-EGFR [8]
  - Antibiotics: Tetracyclines 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
  - Explanations 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

Key points: i) skin rash can be managed with appropriate intervention; ii) erlotinib should be taken at least one hour before or two hours after the ingestion of food.

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 clindamycin 1% gel</td>
<td>Remains 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 1% cream or clindamycin 1% gel or tretinoin 1% cream plus desiccated 100 mg bid or minocycline 100 mg bid</td>
<td>Remains in 2 weeks; if no improvement, treat as severe grade</td>
</tr>
<tr>
<td>Severe</td>
<td>Reduce erlotinib dose for drug inert and monitor for change in severity; continue treatment of rash</td>
<td>Treat as above to moderate grade, and may consider adding methylprednisolone 8 mg 2/3 ho</td>
<td>Reserves in 2 weeks; if necessary, consider dose interruption or discontinuation</td>
</tr>
</tbody>
</table>

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-Empptive Skin Toxicity Treatment With Panitumumab for CRC (STEP) [19]

- Skin therapy consisting of:
  - Moisturizers
  - Sunscreen (PAH-free, SPF ≥ 15, UV-A/UV-B protection)
  - Topical 1% hydrocortisone cream
  - Dexamethasone 100 mg bid
- 95 patients randomized to pre-emptive (24 hr prior to 1st dose) or reactive (after skin toxicity developed)

6-week evaluation

- Pre-emptive
- Reactive

<table>
<thead>
<tr>
<th>Grade</th>
<th>2 skin toxicity (5%) CI</th>
<th>11.35%</th>
<th>40% (76.54%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 skin toxicity (9%) CI</td>
<td>6% (11.3%)</td>
<td>2% (10.3%)</td>
</tr>
</tbody>
</table>

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].

**Anti-EGFR Agents [15, 20]**

- **Cetuximab (Erbitux**®**, Astrazeneca Pharmaceuticals, Wilmington, DE, USA)**
- **Erlotinib (Tarceva**®**, Genentech Inc., South San Francisco, CA, USA)**
- **Gefitinib (Iressa**®**, AstraZeneca Pharmaceuticals, Wilmington, DE, USA)**
- **Lapatinib (GFI-57295; Tykerb®/Tyverb®**, GlaxoSmithKline (GSK), London, United Kingdom)
- **Panitumumab (ABX-EGF; Agemix®, Amgen, Thousand Oaks, CA, USA)**
- **Nimotuzumab (ABX-EGF; Agemix®, Amgen, Thousand Oaks, CA, USA)**
- **EBM 72000 HER1/EGFR**
- **ERB-569 HER1/EGFR**
- **Cetuximab (Erbitux; New York, NY, USA)**

**EGFR Targeted Agents [7]**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>mAb</td>
<td>Locally advanced or metastatic HCC, after at least one prior chemotherapy regimen; locally advanced or metastatic pancreatic cancer in combination with gemcitabine</td>
<td>300 mg/m² every 2 weeks followed by 250 mg/m² every 7 weeks</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>mAb</td>
<td>Locally advanced or metastatic colorectal cancer</td>
<td>300 mg/m² every 2 weeks</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>mAb</td>
<td>Locally advanced or metastatic colorectal cancer in combination with gemcitabine; locally advanced or metastatic pancreatic cancer; locally advanced non-small cell lung cancer</td>
<td>300 mg/m² every 2 weeks</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>mAb</td>
<td>Locally advanced or metastatic colorectal cancer in patients progressing on and intolerant to irinotecan-based chemotherapy</td>
<td>300 mg/m² every 2 weeks</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>mAb</td>
<td>Advanced colorectal cancer patients failing both irinotecan and cetuximab or cetuximab plus irinotecan for first-line treatment of colorectal cancer</td>
<td>12 mg/kg iv bolus followed by 5 mg/kg iv every 2 weeks</td>
</tr>
</tbody>
</table>

**Electronic Communication: A Novel Idea**

- Providing quality health care 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.
**Communication Guide Lines by American Medical Association [29]**

- Establish turnaround times for messages
- Inform patient about privacy issues
- Patients should know who besides doctor processes messages
- Retain electronic and/or paper copies of e-mails communications with patients
- Establish types of transactions and security of subject matter
- Instruct patients to put the category of transaction in the subject line of the message for filtering
- Request that patients put their name and patient identification number in the body of the message
- Develop archival and retrieval mechanisms
- Maintain a mailing list of patients, but do not send group mailings
- Compose messages
- Notify patients to come in to discuss or call them if long e-mails

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**Case #1**

A 67-years-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 86-year-old man with pancreatic cancer on erlotinib called the nurse with irritation in eyes, hoarse voice and mild rash. Patient could not come to see due to a snow storm. He was directed to send a picture of his eyes if possible. Based on the picture, a diagnosis of trichomycosis was made. He was told to get his eyelashes trimmed and use artificial tears. His symptoms improved within 24 hours after the above management.

**Case #3**

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 #4 [1]**

A 36-years-old white female with pancreatic adenocarcinoma stated erlotinib at 150 mg daily. The patient refused to clinic with a palpable periumbilical-anterior rashes on face, neck, hands, widespread erythema on face (Figure). The rash was erythematous, accompanied with dryness, pruritus and tenderness. The scalp, arms, and lower body were not involved. Chest X-ray and chest fluoroscopy revealed no lesion at 150 mg daily were given for 5 months. 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 17 days of use. A week after discontinuation of erlotinib, the patient developed shaking with rigor. Her temperature is only 36.8°C with heart rate of 114/min and respiration rate of 350/min, clinically, the most highly suggestive for pancreatitis infection. A complete blood count revealed leukocytosis with total white cell count of 12,200/μL (reference range: 4,000-10,000/μL), with neutrophil of 77% (reference range: 50-75%). Bone-scans was performed from peripheral bone and double-curve bone-scan. The patient was admitted to hospital and treated with intravenous antibiotics for broad-spectrum with vancomycin and Zosyn® (Piperidinylcarboxamidemethoxy-lactamyl). Two days after treatment, rash was significantly improved after 3 days of anti-biotic treatment and skin lesions resistant but unresponsive-erythematous palpable cyanosis. Fever was removed during that hospitalization, and temporary peripherally inserted central catheter line was removed for acute pancreatitis. Serotonin and active platelet count rose up and peripheral blood cultures were performed. She was treated with benzidamime and prednisolone for at least of 10 days. Topical peripheral blood cultures and cultures from the skin biopsy were performed and sent out. Peripheral blood culture was performed in two days and five days were all negative. The skin rash gradually improved after an discontinuation erlotinib, and eventually disappeared after two weeks of skin care with topical steroids, clindamycin gel.

**Case #5**

This is a Caucasian 64-year-old female with pancreatic cancer who was receiving erlotinib and nab-paclitaxel after failing gemcitabine. She called for a possibility of in grown nail-like problem. She sent us a picture. Diagnosis of paronychia was made and patient was referred to a podiatric as well as started on “per ox” minocycline. She recovered with in 10-12 days.
Case #6

A 72-year-old Caucasian male with pancreatic cancer called in with a rash on the neck and nose, described as dark pigmentation. There was no acne-like rash but only pigmentation was seen. Patient improved his rash on topical clindamycin. The pigmentation totally resolved after he stopped erlotinib (more than 4 weeks later).

Case #6: Few More Examples

Conflict of interest
The authors have no potential conflicts of interest.

References


