EGFRI and Skin Toxicities

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Outline

- Overview of the pharmacology of EGFR inhibitors and associated skin toxicities
- Review of current and new treatment options for EGFR-induced skin toxicities
- Pathophysiology of EGFR inhibitors-induced skin toxicities
- What’s happening at SWOG?

Signal Transduction

Epidermal Growth Factor Receptor or HER1

- Expression of EGFR
- Ligands bind
- EGFR Receptor Dimerization
- Activation of Signal Transduction

Baselga J. J Clin Oncol. 2001;18s:41s-44s.
HER1/EGFR Inhibitors

Two major classes
- Monoclonal Antibodies
  - Cetuximab (Erbitux™)
  - Panitumumab (Vectibix™)
- Small Molecule Tyrosine Kinase Inhibitors (TKI)
  - Erlotinib (Tarceva™)
  - Lapatinib (Tykerb™) – HER1/EGFR & HER2

EGFR Inhibitors - Mechanism of Action
Monoclonal Antibody and Small Molecule TK inhibitor

Antibody Binds
Small molecule EGFR TK inhibitors
Receptor Internalized

EGFR Inhibitor-Induced Dermatological Toxicities

Hair Loss/ Hair Changes
Hyposalivation
Taste Changes
Eye/ Eye Lash Changes
Mucositis
Disruption of normal Hair growth (whole body)
Telangiectasia
Papulopustular Rash
Arterial stenosis
Xerosis/ pruritus
Flushing

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Multinational Association of Supportive Care in Cancer®
EGFR Inhibitor-Induced Skin Toxicity

- Skin toxicities include:
  - Papulopustular rash, hair changes (hair loss, facial hypertrichosis and eyelash trichomegaly), radiation dermatitis, pruritus, mucositis, xerosis and fissures, paronychia

- Papulopustular Rash:
  - Onset: 1-2 weeks
  - Usually occur on face, scalp, and upper body
  - Symptoms: pain/tenderness and pruritus
  - Inflammatory with infectious sequelae

- Papulopustular Rash is common
  - 88% (all grades)
  - 16% (grade 3 or 4) – Dose reduction or discontinuation are recommended
  - Risks:
    - Erlotinib – nonsmokers, fair skin, age >70
    - Cetuximab/panitumumab – male, age <70

- Potential marker for drug activity and clinical outcome

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EGFR-Induced Dermatologic Toxicities

- Paronychia
- Conjunctivities
- Trichomegaly

CTCAE v.4
Rash Acneiform Grading Criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>BSA (&lt;10%)</th>
<th>SX (tenderness, pruritus)</th>
<th>Psychosocial (mood changes)</th>
<th>ADL (IADL)</th>
<th>Infection (+/oral Abx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;10%</td>
<td>±</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>10-30%</td>
<td>±</td>
<td>Yes</td>
<td>IADL</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>&gt;30%</td>
<td>±</td>
<td>±</td>
<td>Self-care ADL</td>
<td>+/oral Abx</td>
</tr>
<tr>
<td>4</td>
<td>Any</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+/IV Abx</td>
</tr>
</tbody>
</table>

Instrumental ADL (IADL) = activities performed by a person who is living independently in a community setting during the course of a normal day, such as managing money, shopping, telephone use, travel in community, preparing meals and doing housekeeping correctly.

Self-Care ADL = ability to perform the most basic physical tasks and personal care activities (i.e., bathing, eating, walking, etc.) independently with or without assistance and without needing another person to do it for you.
**Recommended Treatments for Papulopustular Rash**

- **Mild to moderate:**
  - Cover make-up without worsening the existing rash
  - Standard analgesic for pain
  - Oral antihistamine for pruritus
  - High-potency topical corticosteroids
  - Topical immunomodulatory agent (e.g., pimecrolimus)
  - Avoid topical retinoids and benzoyl peroxide due to skin drying effect
- **Secondary infection:**
  - Prophylactic topical mupirocin
  - Oral antibiotic
- **Severe:**
  - Systemic corticosteroids
  - Interruption of treatment

HER1/EGFR Inhibitor Rash Management Forum Recommendations, Jan 2004

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**Recommended Treatments for Papulopustular Rash**

- **General:**
  - Maintain maximal hydration using emollient cream
  - Sunblock - Sunlight can exacerbate any skin reactions
  - Avoid topical or systemic corticosteroids
- **Grade 1:**
  - Topical anti-acne products
- **Grade 2:**
  - Oral minocycline or doxycycline
  - Oral antihistamine or topical menthol cream for pruritus
- **Grade 3 or 4:**
  - Dosage adjustments
  - Higher doses of oral antimicrobials


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**MASCC Management Guidelines Papulopustular Rash**

- **Prevention**
  - Topical: Hydrocortisone 1% + moisturizer + sunscreen BID
  - Systemic: Minocycline 100 mg PO daily or doxycycline 100 mg PO BID
- **Treatment**
  - Topical: Aclometasone (low) or fluocinonide (hi) 0.05% cream BID, clindamycin 1% BID
  - Systemic: Doxycycline 100 mg BID or minocycline 100 mg PO daily, isotretinoin 20-30 mg PO daily

MASCC Management Guidelines

Hair Changes

- Facial Hypertrichosis
  - Eflornithine 13.9% cream
  - Lasers
- Eyelash Trichomegaly
  - Eyelash trimming regularly
- Alopecia


MASCC Management Guidelines

Paronychia

- Preventive
  - Topical: Diluted bleach soaks, avoid irritants
- Treatment
  - Topical: ultrapotent corticosteroids (e.g. betamethasone), topical calcineurin inhibitors (e.g. pimecrolimus, tacrolimus)
  - Systemic:
    - Tetracycline (empiric) or culture-directed antimicrobials
    - Biotin for brittle nails
  - Other: Silver nitrate chemical cauterization weekly, electrodessication, nail avulsion


What do we know about the pathophysiology of EGFR inhibitor-induced skin rash?

- It is NOT acne or acne vulgaris which has both:
  - Non-inflammatory lesions (comedones)
  - Inflammatory papules, pustules, and nodules caused by bacterial colonization
- Only secondary inflammatory response
EGFR inhibitor-induced Skin Rash

**Histological Characteristics:**
- Suppurative superficial folliculitis
- Lymphocytic perifolliculitis
- No infection etiology

**Proposed MOA:**
- EGFR primarily expressed in undifferentiated, proliferating keratinocytes in the basal and suprabasal layers of the epidermis and the outer layers of the hair follicle
- Expression of EGFR is lost as keratinocytes exit the basal layer
- Inhibition of EGFR in basal keratinocytes leads to follicular degeneration and destruction, causing a strong inflammatory response and release of inflammatory cytokines

Lenz, H et al. Oncology 2006, 20: S2(1-12)
Lacouture M. Nat Rev Cancer 2006, 6(10):803-81

Skin Rash and Clinical Outcomes

- A multivariate analysis of 19 clinical trials and compassionate-use program
- Positive correlation were observed between rash and response/survival in
  - Erlotinib
  - Cetuximab
- Trend between severity of rash and PFS in
  - Panitumumab
- Less consistent results seen in
  - gefitinib


Principles of Skin Rash Treatment

- Elimination of skin rash is not necessarily desirable at this time
- Criteria for optimal supportive treatment:
  - Treatments should not interfere with the anti-tumor effects of EGFR inhibitors
  - Maintain low side effect profile
  - Ease of administration with rapid results to ensure patient compliance
  - Individualize treatment according to presenting sign and symptoms
  - Keep costs at minimal
- Identification of biomarkers that can be obtained with a minimal invasive procedure may be desirable to deliver early or prophylactic interventions
Evaluation of the Current Treatment Recommendations

- Topical anti-acne products
- Topical antibiotic
- Oral antibiotics
- Oral antihistamine
- Topical low or high-potency corticosteroids
- Systemic corticosteroids
- Topical immunomodulatory agent
- Dose reduction or interruption

A Pilot Cross-Over Study to Evaluate the Use of Regenecare® Topical Gel in Patients with Cutaneous Toxicity Caused by Epidermal Growth Factor Receptor (HER1/EGFR) Inhibitors: an Interim Analysis

Siu-Fun Wong, PharmD; Alexander Lindgren, BS; Madhavi Mammaneni, MD; Timothy Byun, MD; Catherine Vasko, RN, MSN, FNP; Rachel Arenos, RN, MSN, FNP; Edward Alexson, MD; and Kathryn Osann, PhD

Journal of Supportive Oncology 2010; 8:202-208

Method

- Patients with grade 2 skin rash (symptomatic) apply Regenecare® Topical Gel to right side of face (3-4 x daily) after rash onset (baseline)
- After 1 week of application, subjects are allowed to cross-over to apply gel to both sides of the face up to a total of 6 weeks

Weekly Assessment:
- Self-reporting by patients
- Clinical grading by provider
- Photos of right and left side of face

Parameters:
- Pain, itching, swelling, redness (Scores: None = 0; Mild = 1; Moderate = 2; Severe = 3)
- Patient product satisfaction survey
Conclusions

- N = 20 enrolled, 13 evaluable
- Reduction in itch at the end of week 1 was greater on the right (treated) side in 69% of patients, on the left (untreated) side in 8%, and the same in 23% (P = 0.01). The pattern was similar for pain, but the differences were not significant.
- Regenecare® topical gel appears effective in relieving EGFR inhibitor-induced skin rash associated pruritus and pain symptoms but minimal/no effect in erythema & swelling.
- The study gel was well tolerated, no adverse effects or secondary infections were noted.
- Pt rated the gel being moderately to extremely effective for alleviating symptoms, improving rash appearance, and easy to apply.

Economic Impact

“Economic impact in the management of dermatologic toxicities (dTs) induced by the epidermal growth factor receptor inhibitor (EGFRI) cetuximab in colorectal cancer.”

N = 29 pts, 99 clinic visits (Mean 3.4/pt)
Visits: $824/visit ($131- 8,451)
Rx: #rx = 9.9/pt; costs = $1,521/pt ($1 - 6,611)
Lab: $188/pt ($0 - 720)
Diagnostic or therapeutic procedures: $238/pt ($0 -1046)

Borovicka JH et al. J Clin Oncol 28:15s, 2010 (suppl; abstr 3569)

Summary

- EGFR inhibitors-induced skin rash should not be treated as acne vulgaris which is bacterial-based.
- EGFR inhibitors-induced skin rash can have significant clinical implications in quality of life and, potential clinical outcome.
- The economic burden contributes markedly to the overall financial burden.
- Current management guidelines continue to lack level I evidence.
- Better symptom management and prophylactic interventions are critical for the minimization of management-related costs.
Current SWOG study

S1013, "A Prospective Study of Epidermal Growth Factor Receptor (HER-1/EGFR) Inhibitor-Induced Dermatologic Toxicity: Validation of the Functional Assessment of Cancer Therapy-EGFRI 18 (FACT-EGFRI 18) Questionnaire for EGFRI-Induced Skin Toxicities”.

Accrual goal = 140 subjects with 112 evaluable

S1013

Primary Objective:
The primary objective of this study is to establish psychometric properties for the Functional Assessment of Cancer Therapy Epidermal Growth Factor Receptor Inhibitor (FACT-EGFRI 18) module (based on criterion validity, known group’s validity, internal consistency reliability, and responsiveness to change) as a patient-reported outcome (PRO) measure of EGFRI-induced skin-related toxicity.

Proposed SWOG Concept

Title: A Phase II Randomized Placebo-Controlled Study to Evaluate the Use of Vit K Topical Lotion in Patients with Cutaneous Toxicity Caused by Epidermal Growth Factor Receptor (HER1/EGFR) Inhibitors

Investigators:
SF Wong, PharmD, J Ryan, PhD, MPH, J Wade, MD, and C Moinpour, PhD
Objectives

Primary Objective: To evaluate the effectiveness of Vit K topical lotion to reduce the severity of EGFRI-induced skin toxicity

Secondary Objective:
- To assess for improvement in subject's QOL and EGFR-inhibitor treatment outcome.
- To evaluate patient tolerability and safety data

Exploratory Objectives

Translational
- Feasibility of less invasive techniques in place of skin biopsy to study biomarkers associated with EGFRI-induced papulopustular skin rash
- Determine the roles of these biomarkers in EGFRI-induced dermatologic toxicity and response to therapeutic intervention

Imaging
- Feasibility and reliability of central reviewer standardized photography protocol

Thank You !!!