

Evaluation of Cutaneous Skin Rash in Subjects Treated with Regenecare™ Topical Gel (Collagen, Aloe vera, & 2% Lidocaine) During Erbitux® and Combination Therapies for Cancer

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Several epidermal growth factor receptor (EGFR) monoclonal antibody drugs are used for the treatment of colorectal, lung, and head and neck cancers. EGFR inhibitors such as cetuximab (Erbitux®), gefitinib (Iressa®), erlotinib (Tarceva®) and the recently approved panitumumab (Vectibix™) are among this group of targeted agents. Skin rash associated with EGFR inhibitors is common since EGFR plays an important role in maintaining the integrity of the skin. Patients usually develop a skin rash within three weeks after the start of treatment with cetuximab.^{1,4} The rash appears as acneform dermatitis accompanied by skin drying, cracking, redness (inflammation), and swelling.² Patients with grade 2 or higher rash usually report pain and itching.

The dermatologic toxicity usually affects the face, upper chest, and back, but occasionally extends to the extremities and generally is not dose limiting. The rash is mostly mild to moderate, but can be more severe in some cases leading to dose reduction, treatment interruption, or treatment cessation. In a clinical trial of 774 patients, 88% of patients undergoing cetuximab plus irinotecan treatment reported an acne-like rash.^{1,3,4,5,6} In addition, 90% of patients receiving cetuximab alone reported acne-like rash.⁶

Presently there is a lack of an evidence-based topical product to treat the skin rash and alleviate the associated symptoms. Relieving the discomfort of the rash is a concern for the medical professionals treating the patient and to maintain patients' quality of life.

Regenecare™ (MPM Medical Inc., Irving TX) is a collagen and aloe vera based wound care gel that contains 2% lidocaine. The product ingredients have been selected based on scientific evidence for wound healing. Collagen has become a valuable component for skin care formulations. It is an effective natural humectant due to an extensive, ordered hydration network that surrounds the molecule while providing high substantivity to the skin surface.⁷ Collagen application has been shown to be safe when applying to skin and has shown improvements in skin integrity and wound repair response when applied.⁸

Although bovine or chicken collagen are typical sources for cosmetic applications, collagens from alternative species may provide benefits as there is less likelihood for transmissible diseases associated with the raw ingredient such as bovine spongiform encephalopathies or avian flu. Regenecare has been formulated with marine collagen for optimal properties without the risks.

Aloe vera gel has also been shown to improve wound healing in several different wound repair models in animals. Aloe vera was shown to improve wound-healing time by increasing microcirculation in animals when applied on second degree burns by both anti-inflammation and wound healing promotion.⁹ Aloe vera stimulated fibroblast proliferation at the wound site when applied to inflamed wounds in mice. Aloe extract is abundant in mannose, lactate and phosphate which help restore the epidermal ion gradient and improve stratum corneum hydration. The mannose phosphate complex may possibly act to stimulate the growth-repair response and anti-inflammatory activity as seen in animal models of damaged and inflamed skin.¹⁰ Aloe vera treated wounds synthesize greater amounts of type III collagen and its organization, important for establishing wound structure, guiding inflammatory cells and fibroblasts into the wound site and providing a matrix for re-establishment of blood supply.¹¹

Lidocaine is a local anesthetic. Lidocaine, at concentrations of 2% to 5% solutions, are safely used in topical products to alleviate pains associated with burns and scrapes.¹²

Purpose

The purpose of these case observations was to determine if Regenecare topical gel applied to EGFR inhibitors-induced rash improved patient symptoms such as pain, itching, redness (inflammation) and skin integrity. Case II received combination therapy of Erbitux and chemotherapy agents (docetaxel and carboplatin). Case III received Erbitux with external beam radiation to the right side head and neck region.

Method

Following informed consent, subjects who experienced Erbitux-induced dermatitis were instructed to apply Regenecare gel to the right side of the face only and had the option of requesting to cross over and use product on both sides of face after a minimal of 1 week. Patients are required to inform the health care provider at the office visit before cross-over can occur. Grading of the skin was assessed by a self-directed patient questionnaire and independently by the health care provider to determine degree of itching, pain, swelling and redness every week upon the onset of rash (week 1). Pictures were taken of both sides of the face weekly at a distance of 12" to 18" at the same setting using a H.P. Photosmart digital camera (5.2 megapixels).

Case Subject II Receiving Erbitux, docetaxel and carboplatin

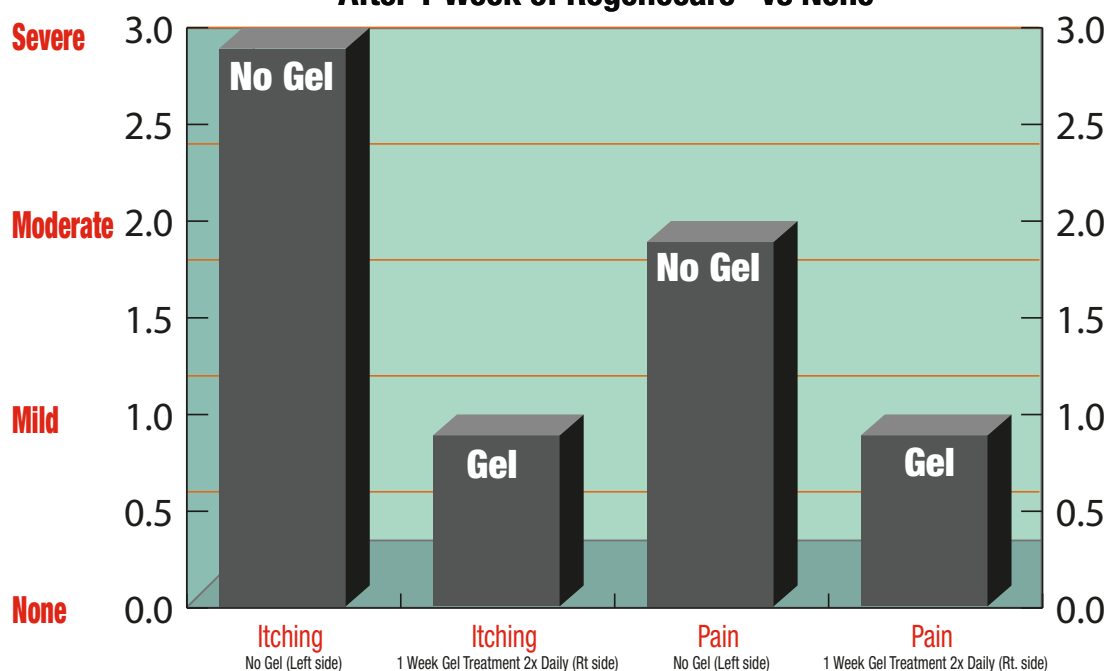
Case II is a 57 year old male with recurrent laryngeal squamous cell carcinoma receiving weekly cetuximab in combination with q 3-week docetaxel and carboplatin. Subject developed skin rash after loading dose (800 mg) of cetuximab and was instructed to apply Regenecare Wound gel three times a day to right side of the face only using standardized instructions. Subject was assessed after 2 treatments of cetuximab (800 mg & 500 mg) and reported a difference of itching score of 3 vs 1, and pain score of 2 vs 1 on the left side and the right side of the face, respectively. Of note is this subject was found to be non-compliant and only apply the Regenecare twice a day.

| | Baseline Week 1 | | Week 2 | | Week 3 | |
|----------|-----------------|----------------|---------------------|----------------|---------------------|--------------------|
| | Right No gel | Left No gel | Right Gel 2x/day | Left No gel | Right Gel 2x/day | Left Gel 2x/day |
| Itching | 0 | 0 | 1 | 3 | 1 | 1 |
| Swelling | 0 | 0 | 0 | 0 | 0 | 0 |
| Redness | 2 | 2 | 2 | 2 | 1 | 1 |
| Pain | 0 | 0 | 1 | 2 | 1 | 0 |

Rating Score: 0 = None; 1 = Mild; 2 = Moderate; 3 = Severe

Case II

Pain and Itching Scoring of Erbitux® Rash After 1 Week of Regenecare® vs None



Case II Photos



Week 2: (rash flare) right side, **one week gel treatment**, 2 x daily, mild itching, mild pain, moderate redness. Grade 2 clinical rash.



Week 2: (rash flare) left side, **no gel**, severe itching, no pain, moderate redness. Grade 2 clinical rash.



Week 3: right side, **2 weeks gel treatment**, 2x daily, mild itching, mild pain, mild redness. Grade 1 clinical rash.



Week 3: left side, **1 week gel treatment**, 2x daily, **crossed over**, mild itching, no pain, mild redness. Grade 1 clinical rash.

Unretouched Photos

Case III Subject Receiving Erbitux and Radiation Therapy

Case III The subject was a 53 year old Caucasian male diagnosed with head and neck cancer undergoing treatment with a combination of Erbitux and external beam radiation therapy. After receiving a loading dose of 800mg of Erbitux, the patient continued to receive maintenance doses of Erbitux at 500mg on a weekly schedule for the duration of his radiation treatments. Patient received a total of 4680 cGy to the right tonsillar and pharyngeal region over 5 weeks followed by interstitial implantation of the right neck and right tonsillar with iridium-192 brachytherapy 2 weeks after completion of radiation.

Results of Case III (Erbitux and Radiotherapy) Patient Self-Assessment Scoring of Rash Symptoms

| | Baseline Week 1 | | Week 2 | | Week 3 | |
|---------|-----------------|----------------|---------------------|----------------|---------------------|--------------------|
| | Right No gel | Left No gel | Right Gel 4x/day | Left No gel | Right Gel 6x/day | Left Gel 6x/day |
| Itching | 1 | 0 | 0 | 2 | 0 | 0 |
| Redness | 1 | 1 | 2 | 2 | 1 | 1 |
| Pain | 1 | 0 | 1 | 1 | 1 | 1 |

Rating Score: 0 = None; 1 = Mild; 2 = Moderate; 3 = Severe

National Cancer Institute Toxicity Criteria Version 3.0 Grading Descriptive Criteria

| Acneform Rash/Desquamation | | | |
|---|---|--|---|
| Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Macular or papular eruption or erythema without associated symptoms | Macular or papular eruption or erythema with pruritis or associated symptoms; localized desquamation or other lesions covering < 50% of body surface area | Severe, generalized erythroderma macular, papular, vesicular eruption; desquamation covering >= 50% of body surface. | Generalized exfoliative, ulcerative or bullous dermatitis |

Clinical Skin Assessment Receiving Erbitux and Radiotherapy to Right Side of Head and Neck

| | Baseline Week 1 | | Week 2 (rash flair) | | Week 3 | | Week 4 | |
|-----------|--------------------------------------|----------------|--|----------------|--|--------------------|--|--------------------|
| | Right (irradiated side) No gel | Left No gel | Right (irradiated side) Gel 4x/day | Left No gel | Right (irradiated side) Gel 6x/day | Left Gel 6x/day | Right (irradiated side) Gel 6x/day | Left Gel 6x/day |
| NCI Scale | Grade 2 | Grade 1 | Grade 2 | Grade 2 | Grade 1 | Grade 1 | Grade 1 | Grade 1 |

Conclusion

Combining chemo- and radio- therapies becomes an even greater challenge to the clinician to ease the discomfort for the patient and control the breakdown of the skin which has impaired wound healing mechanisms due to the treatments. The case results are of interest to the clinician in that there was an overall stabilization and improvement from a grade 2 rash down to a grade 1 rash/erythema condition, which was maintained with continued Regenecare gel application in both cases. Pain and itching scoring was improved in both cases, 1 to 2 levels lower (moderate to none, moderate to mild, severe to mild) during application when applied to either side of face during either chemo- or radiation treated Erbitux patients. These pre-pilot observations of an ongoing clinical study are presented for observation of Regenecare in the clinical management as an adjuvant skin therapy for symptoms of EGFR rash management.

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