A Pilot Study to Determine the Effectiveness of a Topical Gel with 2% Lidocaine-HCl, Collagen, Hyaluronic Acid and Aloe Extract for Treatment of Adverse Rash Symptoms Associated with HER1/EGFR Inhibitors

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Abstract

Significance and Background: Targeted Epidermal Growth Factor Receptor (EGFR) inhibitors drugs have emerged as important and effective therapies to treat colorectal, lung, and head and neck cancers. They have a more tumor-specific and more manageable toxicity profile than traditional chemotherapy. Despite these benefits, a commonly occurring side effect is the appearance of an acneform rash in over 85 percent of treated patients on face, arms, chest, legs and back. This adverse event can result in treatment dose reduction, interruption, and cessation. Clinicians need clinical strategies for managing the adverse side effects.

Purpose: The purpose is to provide evidence based adjunct therapy to treat rash symptoms at its earliest onset for optimum patient management.

Interventions: A single center, prospective pilot study of 20 EGFR-inhibitor treated patients were enrolled to evaluate Regenecare HA™ for reducing itching and pain associated with EGFR rash. Regenecare™, an original wound gel formula was clinically evaluated in a cross-over trial. Published results of two clinical pilot studies showed significant reduction of pain and itching with gel use. Feedback from patients as expressed to clinical nurses in two pilot studies, however, indicated that the original gel was somewhat drying. The manufacturer adjusted the formula by adding a moisturizer (Hyaluronic acid) to improve patient compliancy and use without modifying the active ingredient, 2% Lidocaine-HCl. Participants were instructed to apply gel four times daily to rash areas during treatment cycle. Nurses assessed rash severity weekly using NCI CTCAE version 3. Patients responded weekly for 4 weeks of application during treatment cycle to questionnaires. Original data was evaluated as percentage outcome and reported.

Evaluation: Eighteen subjects' questionnaires and nurses' evaluations were collected and calculated as a percentage of each response. Patients reported the gel as 88.8% effective for reducing appearance, 86.6% effective for reducing itching, 87.5% effective for reducing pain and 94.1% effectiveness towards skin healing.

Discussion: Evidence-based symptom management is important for clinicians to offer patients with EGFR-inhibitor induced rash. The clinical results indicated the gel is a safe and effective adjunct therapy for managing Grade 1-2 rash symptoms for out-patient care.

Introduction

Epidermal Growth Factor Receptor (EGFR) Inhibitors drugs such as erlotinib (Tarceva), cetuximab (Erbitux) and gefitinib (Iressa) are used to treat various colorectal, lung and head and neck cancers. EGFR drugs target epidermal derived tissues including capillaries, sebaceous cells, hair shaft and hair follicles. This targeted bioreaction causes a severe acneform rash in over 80 percent of treated patients occurring on face, arms, chest, legs and back (Wong et al, 2007). The rash is red, inflamed, pustular, and can be painful. The primary symptom reported from patients experiencing grade 1-3 rash is itching (puritis). In order to support patients' comfort and quality of life during treatment, physicians and nurses need an evidence based product to help relieve itching and pain. A topical wound gel (Regenecare Wound Gel) containing 2% Lidocaine in a base of collagen and aloe vera extract was proposed to provide some relief and was tested in several controlled clinical pilot studies. The wound gel showed statistical significance for reducing both pain and itching in a pilot cross-over trial (Wong et al, 2007). Another clinical pilot study with patient product evaluations use for 6 weeks, reported substantial symptom relief with product use for EGFR rash, as well (Gowland et al, 2008, Kozloff et al, 2007). Regenecare is originally formulated for deep wounds and 2nd degree burns. The investigators noted the clinical results indicated the gel very effective towards pain and itching, yet some patients noticed the product felt dry after application especially to the face. The manufacturer (MPM Medical Inc., Irving Texas) modified the product formulation by adding an effective moisturizer (Hyaluronic acid) to better accommodate the needs of the patients specifically using the gel for epidermal rash. Hyaluronic acid is the most hygroscopic moisturizer occurring naturally on the skin. It was of importance to conduct a clinical study in which patients used the Hyaluronic acid containing Lidocaine-HCl gel for its effectiveness towards symptoms of EGFR rash.

Methods

A single center prospective clinical study was undertaken to observe patients treated with gel application towards EGFR inhibitors induced rash. Patients selected met criteria of over 18 years of age, to be started on EGFR inhibitors therapy, having no serious concomitant skin disorders and likely to comply. After obtaining signed informed consent, patients were instructed to apply the reformulated gel 4 times daily to rash for 4 weeks. Of twenty patients selected eighteen were chosen for outpatient product use during 6 weeks of EGFR inhibitors drug treatment. The gel contains 2% Lidocaine HCL, hyaluronic acid, aloe extract and marine collagen (RegenecareHA, MPM Medical Inc. Irving, TX). Typically the rash appears the second week of EGFR/HER1 treatment. Nurses graded the rash according to the skin toxicity scale (grade1-4). Patients evaluated rash symptom relief for reducing appearance (redness and inflammation), reducing itching, reducing pain, and for skin healing. Subjects rated gel as to its effectiveness for reducing symptoms as "effective" or "not effective" towards reducing each symptom. If a symptom was not experienced, patients' responses were counted as not applicable.

Gowland et al. (2008) conducted and published the same clinical pilot product evaluation study for Regenecare (original) topical application for patients experiencing EGFR inhibitors induced rash. Selection criteria, consent forms, IRB approval, clinical protocol, study location (Ingalls Cancer Center), patient instructions, gel application schedule, and product evaluation questionnaires were the same. Patients applied Regenecare original gel to their rash six weeks during EGFR inhibitors drug treatment schedule. Similar to this trial, eighteen subjects completed the trial and were evaluated. The ordinate data is evaluated for all groups using the same responses and grouped for effectiveness evaluation for each symptom. Thus the questionnaire responses for moisturizing effects and other rated symptoms of both products can be correctly related and compared graphically.

Results

Regenecare HA was rated by 100% of patients as an effective moisturizer. It appears that the addition of Hyaluronic acid did provide substantial moisturizing effect. The prior Gowland et al. study (2008) with Regenecare original showed only a 55% patient response as effective as to moisturizing (ref). Additionally, patients' responses as to gel effectiveness for "reducing rash appearance" was increased by 30% with the use of RegenecareHA as compared to Regenecare original. These results support the fact that the addition of hyaluronic acid to the original 2% Lidocaine HCl, collagen and aloe topical gel formula was an improvement because it was more effective than the prior formulation. (Graph 1).

Hyaluronic acid has been reported in the literature to be the most hygroscopic moisturizer commercially available as it is the skin's naturally occurring moisturizer. Continuous topical application of hyaluronic acid has been reported to enhance epidermal repair and healing mechanism when the epidermis has been damaged with heat, radiation or wounding (Gao et al, 2011). It enhances fibroblast production and migration in the wound. This improved formula could enhance patient compliancy by their regular use of the product during EGFR rash. It supported an improvement in skin condition and therefore quality of life of patients undergoing EGFR treatment regimens experiencing the rash.

Regenecare HA was rated showing that 88.8% of patients reported it effective in treating rash appearance, 86.6 % patients reported effectiveness in relieving pain, 87.5% patients reported effectiveness for relieving itching and 92.1% of patients reported effectiveness for skin healing.

Conclusion

Overall both products' patient evaluations were very similar for symptom relief of pain, itching, and skin healing. Results of the second trial with reformulated Regenecare HA indicated a more positive result for the parameters of "reducing appearance" and for "moisturizing" the drying rash condition. (Graph 3). These results indicate that the formula was substantially improved by adding the hyaluronic acid moisturizing ingredient for rash treatment. The addition of the moisturizing ingredient showed a substantial increase in patient responses for reducing the redness and inflammation, designated as "reducing rash appearance" and for its "moisturizing" effect on the skin as compared to the prior product. It is well established in dermatology literature that moisture improves wound healing outcomes (Svensjö et al, 2000). Observing patients positive responses that gel application reduced redness and inflammation suggests moisturizing and healing properties of gel ingredients. RegenecareHA is one of few evidence-based topical products that can be used as an adjunct treatment for symptoms in patients experiencing Grade 1 and 2 EGFR inhibitors induced rash.

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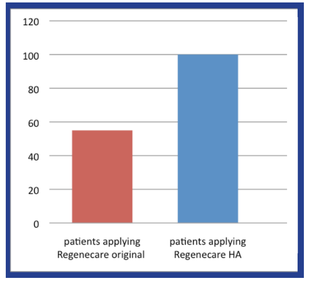
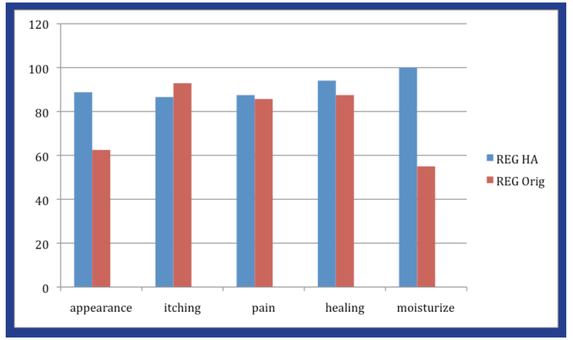


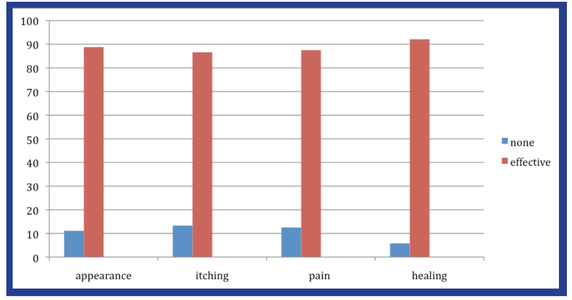
Graph 1

Percentage of Patients Applying Regenecare™ Original vs. Regenecare™HA for EGFR Rash Rating Effective for Skin Moisturizing
100% of Patients Applying Regenecare™ HA rated it Effective as a Moisturizer as Compared to 55% of Patients rated Regenecare™ Original as Effective as Moisturizer



Graph 2

Percentage Patients Reporting Regenecare™ HA (REG HA) and Regenecare Original (REG Orig.) Effective for Rash Symptom Relief Using the Same Clinical Protocol and Patient Questionaires (N=18) for each trial (N=36) total patients



Graph 3

Percentage of Subjects that Evaluate Regenecare™ HA Topical Gel Effective for Rash Symptoms for Reducing Appearance, Itching, Pain and for Skin Healing During 6 weeks of EGFR-Inhibitors Drug Treatment