Effects of Colloidal Oatmeal Lotion on Symptoms of Dermatologic Toxicities Induced by Epidermal Growth Factor Receptor Inhibitors

Ya-Ting Ke, RN, and Chia-Chi Kuo, RN

ABSTRACT

OBJECTIVE: The common adverse effects associated with targeted therapy for cancer, such as epidermal growth factor receptor inhibitors (EGFRIs), are dermatologic toxicities that cause the patient physical discomfort and affect treatment. Colloidal oatmeal lotion (COL) has been proven to help prevent dermatitis and xerosis. Evidence of its effect on EGFRI-induced dermatologic toxicities, however, is limited. The purpose of this study was to explore the effect of COL on EGFRI-induced dermatologic toxicities.

DESIGN AND SETTING: This study used a 1-group pretest-posttest design with a convenience sample of 30 patients with cancer who developed EGFRI-induced dermatologic toxicities from a medical center in southern Taiwan. All participants applied topical COL 3 to 5 times a day for 4 consecutive weeks and received a pretest and 4 posttests.

OUTCOME MEASURES: A generalized estimating equation was used to assess the impact of demographics, disease characteristics, and weeks of COL use on dermatologic toxicity severity, body surface area affected, and level of pruritus.

MAIN RESULTS: Significant differences were found between the pretest and all posttests after using COL with regard to the severity, body surface area affected, and level of pruritus in participants who developed EGFRI-induced dermatologic toxicities ($P < .05$). There were no significant differences in demographics or disease characteristics on EGFRI-induced dermatologic toxicities.

CONCLUSIONS: Based on the study results, COL could improve the symptoms of dermatologic toxicities in those receiving EGFRIs with no adverse effects. Therefore, the authors suggest the use of COL in clinical settings.

KEYWORDS: colloidal oatmeal lotion, epidermal growth factor receptor inhibitors, pilot study, symptoms of dermatologic toxicities, targeted therapy

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INTRODUCTION

Cancer treatment and management of the resulting adverse effects are global healthcare issues.[1] Targeted therapy, a newer type of cancer treatment that more precisely targets tumor cells to block their growth and spread, is considered to be less harmful to normal cells than traditional chemotherapy and radiation treatment.[2,3] Although devoid of systemic toxicities, the use of targeted therapies, especially epidermal growth factor receptor inhibitors (EGFRIs), is associated with dermatologic toxicities,[4] which cause discomfort and negatively affect adherence with EGFRI therapy.[5] These common adverse effects include folliculitis (present as acneiform rash, acneiform eruption), xerosis (present as dry, rash, itchy, scaly, and distal fissuring), paronychia, and hair changes.[6,7] A clinical follow-up study reported on an incidence of folliculitis of 94% and xerosis of 100% in patients treated with EGFRIs.[6] Dermatologic adverse effects do not directly jeopardize patient safety, but may affect patients' quality of life and even decrease their willingness to continue to receive targeted therapy.[2,4,5,8] Moreover, oncologists may perform dose reductions or discontinuation of EGFRIs to avert dermatologic toxicities, which indirectly compromises the effectiveness of targeted agents.[9,10] In response to these factors, the dermatologic disorders induced by EGFRIs should be properly managed clinically.

The mechanism of EGFRI-induced dermatologic toxicities is to interrupt the normal growth and differentiation of the epidermis, thereby leading to dermatologic signs such as hyperkeratosis,

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xerosis, inflammation, and hypersensitivity responses.[5,8,11] The common management for these dermatologic disorders is the use of keratolytic agents, topical moisturizers, corticosteroids, antibiotics,[4,5,7] antihistamines, isotretinoin, and antiacne medications.[5,7] However, the effect of these management strategies is limited.[6,12] Moreover, the majority of patients suffer from the adverse effects caused by long-term exposure to chemical preparations and medications, as well as the resulting financial burden.

Consequently, researchers have introduced the development and application of natural products such as colloidal oatmeal. Colloidal oatmeal is produced by finely grinding oats and boiling them to extract the colloidal material, which has been used for treating skin conditions since 1945[13,14] and was approved by the Food and Drug Administration as a skin protectant in 2003.[13,15] Colloidal oatmeal contains many components with different skin benefits as follows: proteins, starches, polysaccharides, essential fatty acids, phospholipids, and β-glucan reinforce the skin's protective and moisture barrier[13,14,16,17]; saponins contribute to the cleansing activity[13]; oat phenols, β-glucan, and flavonoids improve anti-inflammatory, calming, and soothing effects[14,17]; and phenols, especially avenanthramides, vitamin E, and ferulic acid strengthen antioxidant/anti-inflammatory effect and alleviate xerosis and inflammation.[14,15] Colloidal oatmeal lotion (COL) has cleansing, moisturizing, buffering, protecting, anti-irritation, anti-itch, antioxidant, anti-inflammatory,[13,14,18] and skin-repairing properties[19] and is commonly applied to improve conditions such as red, dry, itchy, irritated, and inflamed skin, as well as acneiform eruptions.

In June 2013, the authors searched for relevant systematic reviews in 7 English and Chinese language databases, including Airiti Library, CINAHL, Cochrane Library, EBSCO, Index of Taiwan Periodical Literature System, National Digital Library of Theses and Dissertations in Taiwan, and PubMed/MEDLINE by using the following keywords and terms: ("target therapy" or "epidermal growth factor receptor inhibitors" or "EGFRIs") and ("oatmeal lotion" or "colloidal oatmeal"). They restricted the search to "human," "adult," "randomized controlled trial," or "clinical trials." Search results yielded only 1 interventional study regarding the application of colloidal oatmeal to EGFRI-induced dermatologic toxicities. The study, conducted by Alexandrescu et al[20] examined 10 patients who developed acneiform or papular eruption induced by EGFRIs. The results showed that continuous topical use of COL significantly improved EGFRI-induced dermatologic toxicities. Generalizability of the results is limited, however, because of the small sample size and lack of objective pretest-posttest comparison data. Therefore, the authors used a 1-group pretest-posttest pilot study design to examine the improvement effect of COL on severity, body surface area affected, and pruritus induced by EGFRIs during the 4-week intervention. The findings are expected to serve as a reference for clinical practice and future formal research.

METHODS

Design, Setting, and Sample

This pilot study used a 1-group pretest-posttest design with a convenience sample of 30 patients with cancer who developed EGFRI-induced dermatologic toxicities from a medical center located in southern Taiwan. The authors conducted a pretest and 4 consecutive weekly posttests. Inclusion criteria were (1) patients with cancer receiving an EGFRI treatment regimen and experiencing dermatologic toxicities (redness, rash, papules, acneiform rash, pustules, xerosis, pruritus); (2) being 20 years or older and without visual, hearing, and/or mental impairments; and (3) being conscious and able to communicate either by speaking Mandarin or Taiwanese. Exclusion criteria were patients who met inclusion criteria but had received dermatologic treatment or had stopped EGFRI treatment regimen during the study period.

Intervention Program

Each participant who experienced dermatologic adverse effects after receiving EGFRI-targeted therapy applied a reasonable amount (complete coverage of lesions) of COL (Reto; Kutol Products Company, Sharonville, Ohio) on each affected site 3 to 5 times a day for 4 consecutive weeks. Ehmann et al[2] suggested that liberal use could enhance the moisturizing effect of COL and improve xerosis, and 1 dermatologist (Feng YH) recommended 3 to 5 times/day use based on clinical experience. Accordingly, the authors asked participants to apply COL at least 3 times and up to 5 times a day, according to their level of dry and itchy sensation. The COL used in this current study was composed of active ingredients, including hydrolyzed oat protein, oat phenols, and β-glucan, which contribute to the calming, soothing, moisturizing protective, and anti-inflammatory effects on the skin.

Data Collection and Ethical Considerations

This study was approved by the institutional review board (IRB10011-005) of the study hospital in southern Taiwan. The study period was from November 1, 2011, to August 31, 2013. In the beginning of the study, the authors explained the purpose, procedure, and cooperating matters of the study to all participants. Prior to data collection and intervention, participants were asked to sign an informed consent form. All collected data were coded, kept confidential, and used only for the study purpose.

Instruments

To ensure intrarater reliability, all data measurement and collection were performed by the same researcher. The measuring instruments and their reliability and validity were described as follows:

• Dermatologic Toxicity Severity Scale: Because of the difficulties in using existing scales to objectively measure the improvement trend of EGFRI-induced dermatologic toxicities, the research team developed a dermatologic toxicity severity scale based on the literature review[2,21] and their clinical experience. They revised the scale according to the expert opinions of 2 physicians specialized in targeted therapy, 1 dermatologist, and 5 registered nurses in the cancer unit. All participants underwent whole-body dermatologic examinations and were scored for the site with the most severe dermatologic toxicity on a scale from 0 (lowest) to 10 (highest): 10 = acneiform rash accompanied with pustules eruption; 9 = acneiform rash accompanied with xerosis or crusted pustules; 8 = mostly acneiform rash; 7 = approximately half acneiform rash and half papules; 6 = massive inflammatory papules; 5 = approximately half papules and half rash; 4 = massive rash accompanied with limited xerosis or crusted papules; 3 = mostly crusting papules accompanied with limited rash; 2 = xerosis and redness accompanied with new rash; 1 = all crusted rash without xerosis, redness, or rash; and 0 = crusts fallen off or no dermatologic signs.

• Body Surface Area Affected by Dermatologic Toxicities: Each week, the researcher took pictures of participants' whole-body dermatologic signs with the same digital camera and measured the length and width of each dermatologic sign with the same measuring tape. The authors used ImageJ analysis software (https://imagej.nih.gov/ij), a widely used, freely available image analysis software,[22] to calculate the body surface area of irregular shape of each dermatologic sign (Figure 1) and then summed the areas of all signs to produce a total body surface area associated with dermatologic toxicities for each participant for the current week.

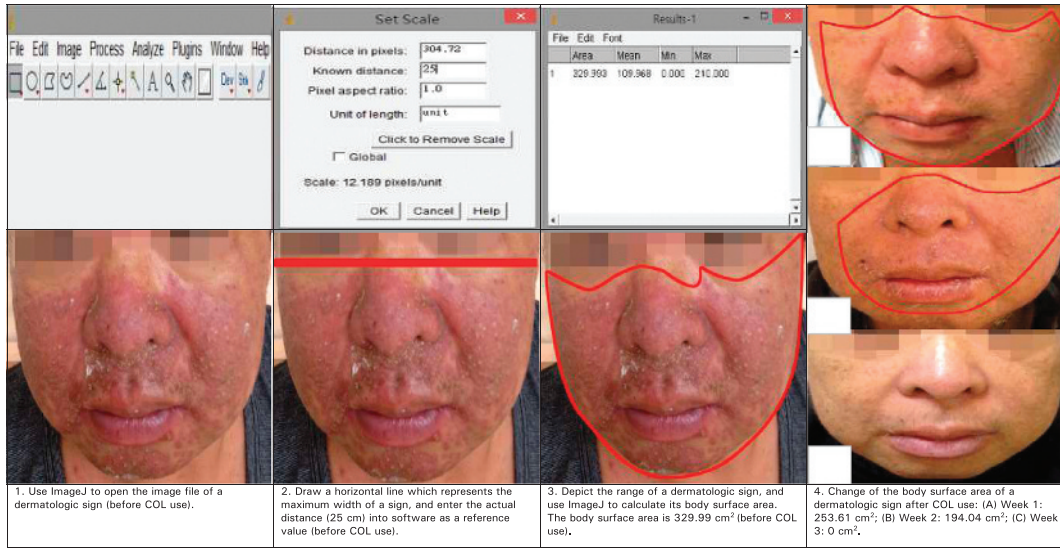
• Pruritus Scale: The researcher measured the participants' level of pruritus using a 10-cm visual analog scale developed by Gift,[23] where 0 refers to no pruritus at all, and 10 refers to worst possible pruritus. The level of pruritus was assessed as reported by each participant on the 10-cm scale to represent each one's perception of pruritus for the current week.

Statistical Analyses

The raw data were coded and entered into Excel and were analyzed using SPSS for Windows version 18.0 (SPSS Inc, Chicago, Illinois). Independent *t* tests and analyses of variance were used to evaluate the impact of different demographics and disease characteristics on the mean pretest scores regarding dermatologic toxicities. Seven of the 30 participants did not complete dermatologic assessment at planned follow-up visits and generated a total of 12 missing values at the 4 posttests. In accordance with the principles of intention-to-treat analysis, a generalized estimating equation (GEE) was used to accurately estimate the

Figure 1.

INSTRUCTIONS TO USE IMAGEJ ANALYSIS SOFTWARE TO CALCULATE THE BODY SURFACE AREA OF IRREGULAR SHAPE OF EACH DERMATOLOGIC SIGN



Abbreviation: COL, colloidal oatmeal lotion.

Table 1.

DISTRIBUTION OF DEMOGRAPHICS AND DISEASE CHARACTERISTICS AND THEIR IMPACT ON DERMATOLOGIC TOXICITY PRETESTS (N = 30)

	Frequency Distribution		Dermatologic Toxicity Severity Scale (score)		Body Surface Area Affected by Dermatologic Toxicities (cm^2)		Pruritis Scale (score)	
Variables	**n**	**%**	**mean ± SD**	***P***	**mean ± SD**	***P***	**mean ± SD**	***P***
Age range (years)				.229[b]		.364[b]		.016[b,d]
① 21–40	9	30.00	8.00 ± 1.94		295.06 ± 301.67		1.00 ± 1.43	
② 41–60	16	53.33	6.44 ± 2.68		712.56 ± 1332.24		3.83 ± 2.86	
③ >61	5	16.67	6.00 ± 2.24		43.19 ± 24.71		1.16 ± 1.77	
Sex				.595[a]		.182[a]		.903[a]
① Female	16	53.33	7.06 ± 2.41		243.39 ± 511.67		2.51 ± 2.74	
② Male	14	46.67	6.57 ± 2.59		741.29 ± 1350.26		2.63 ± 2.68	
Primary tumor site				.134[b]		.864[b]		.548[b]
① colorectal cancer	19	63.33	7.21 ± 2.20		580.77 ± 1211.70		2.07 ± 2.92	
② breast cancer	2	6.67	4.00 ± 2.83		53.87 ± 53.03		4.55 ± 2.62	
③ lung cancer	4	13.33	5.25 ± 3.40		464.16 ± 823.19		3.25 ± 2.22	
④ multiple sites of cancer	5	16.67	7.80 ± 1.79		254.66 ± 226.69		3.10 ± 1.94	
EGFRIs				.066[b]		.836[b]		.456[b]
① Erbitux	24	80.00	7.33 ± 2.10		512.83 ± 1084.57		2.28 ± 2.74	
② Herceptin	2	6.67	4.00 ± 2.83		53.87 ± 53.03		4.55 ± 2.62	
③ Iressa	4	13.33	5.25 ± 3.40		464.16 ± 823.19		3.25 ± 2.22	
Number of areas affected by dermatologic toxicities				.755[b]		.011[b,c]		.799[b]
① 1 area	13	43.33	7.23 ± 2.59		125.53 ± 124.36		2.34 ± 2.89	
② 2 areas	8	26.67	6.50 ± 1.93		139.54 ± 214.15		2.35 ± 1.59	
③ ≥3 areas	9	30.00	6.56 ± 2.88		1280.46 ± 1606.49		3.08 ± 3.27	

[a]*P* value of Independent *t* tests; [b]*P* value of analysis of variance (ANOVA); [c]Bonferroni post hoc test: ③>②,①; [d]Bonferroni post hoc test: ②>①
Abbreviation: EGFRIs, epidermal growth factor receptor inhibitors.

effects of repeated-measures variables between weeks.[24] Statistical significance was set at $\alpha < .05$.

RESULTS

Baseline Characteristics

The distribution of demographics and disease characteristics and impact on dermatologic toxicity pretests are summarized in Table 1. The results of the impact of demographics and disease characteristics on mean pretest scores regarding dermatologic toxicities showed that there were only significant differences in the mean pretest scores for pruritus among age groups ($P = .016$) and in the mean pretest scores for body surface area affected among the number of areas affected by dermatologic toxicities ($P = .011$).

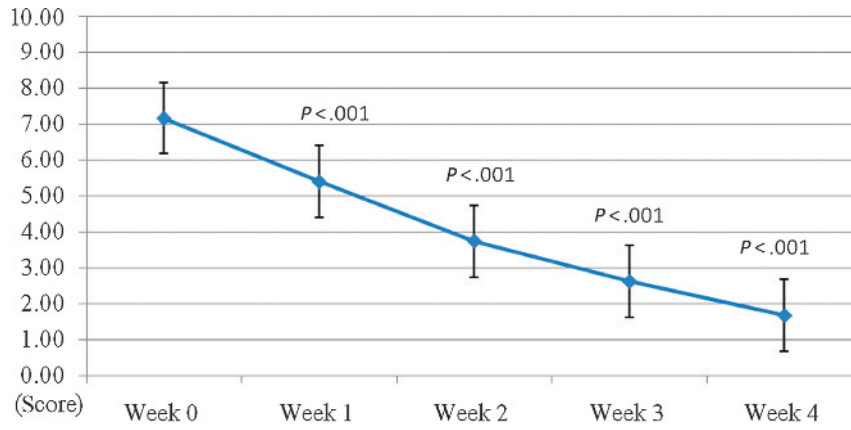
Table 2.

GENERALIZED ESTIMATING EQUATION OF THE IMPACT OF DEMOGRAPHICS, DISEASE CHARACTERISTICS, AND WEEKS OF INTERVENTION (N = 30)

	Dermatologic Toxicity Severity Scale		Body Surface Area Affected by Dermatologic Toxicities		Pruritis Scale	
Variables	**B**	***P***	**B**	***P***	**B**	***P***
Intercept	1.79	.870	288.75	.650	7.97	.137
Time						
week 1 vs. week 0	−1.77	<.001	−120.80	.024	−.91	.008
week 2 vs. week 0	−3.42	<.001	−251.47	.024	−1.33	.001
week 3 vs. week 0	−4.55	<.001	−341.16	.006	−1.71	<.001
week 4 vs. week 0	−5.50	<.001	−395.01	.002	−1.85	<.001
Age	.01	.896	−3.12	.695	−.04	.424
Sex	−.04	.610	3.14	.749	.03	.485
Primary tumor site	.08	.621	−2.17	.818	−.08	.327
Type of EGFRI	−.03	.594	−4.44	.828	.00	.924
Number of areas affected by dermatologic toxicities	.18	.590	6.43	.511	−.16	.363

Setting age, sex, primary tumor site, type of EGFRI, and number of areas affected by dermatologic toxicities as covariances.
Abbreviaion: EGFRI, epidermal growth factor receptor inhibitor.

Figure 2.
GENERALIZED ESTIMATING EQUATION MODEL ANALYSIS OF DERMATOLOGIC TOXICITY SEVERITY SCALE



GEE Analysis

Considering that 7 of the pooled participants, respectively, produced 1 to 3 missing values for the posttests, the authors used the GEE model, setting pretests as reference groups and age, sex, primary tumor site, type of EGFRI, and number of areas affected by dermatologic toxicities as covariances. The results are shown in Table 2 and Figures 2 to 4.

The results of the GEE analysis showed significant improvement in dermatologic toxicity severity after continuous use of COL for 1, 2, 3, or 4 weeks as compared with pretests ($P < .001$). However, there were no significant differences in the impact of demographics and disease characteristics on dermatologic toxicity severity ($P > .05$). The dermatologic toxicity severity reduced from a pretest score of 7.16 ± 1.66 (mean ± SE) to a posttest score of 5.40 ± 1.51 ($P < .001$) at week 1, 3.74 ± 1.53 ($P < .001$) at week 2, 2.62 ± 1.58 ($P < .001$) at week 3, and 1.67 ± 1.55 ($P < .001$) at week 4 (Figure 2). The results indicated that there were significant differences between pretests and all 4 weekly posttests. The participants' dermatologic toxicity severity was significantly improved in the first week and sustained reductions over time from the mean pretest score of 7.16 (approximately half acneiform rash and half papules) to the mean posttest score of 1.67 at week 4 (all crusted rash without xerosis, redness, or rash), or nearly complete remission.

The GEE analysis showed a significant reduction in the body surface area affected by dermatologic toxicities after continuous

Figure 3.
GENERALIZED ESTIMATING EQUATION MODEL ANALYSIS OF BODY SURFACE AREA AFFECTED BY DERMATOLOGIC TOXICITIES

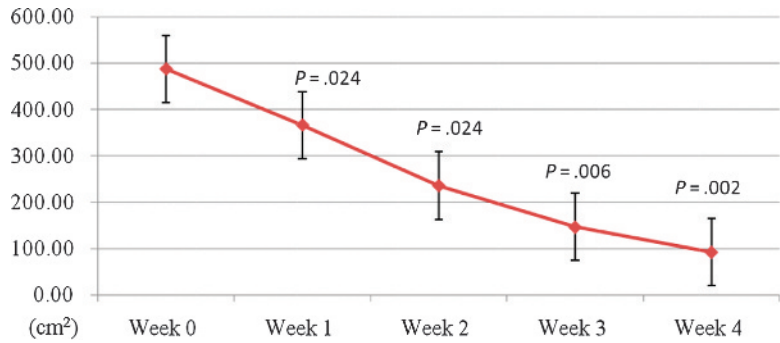
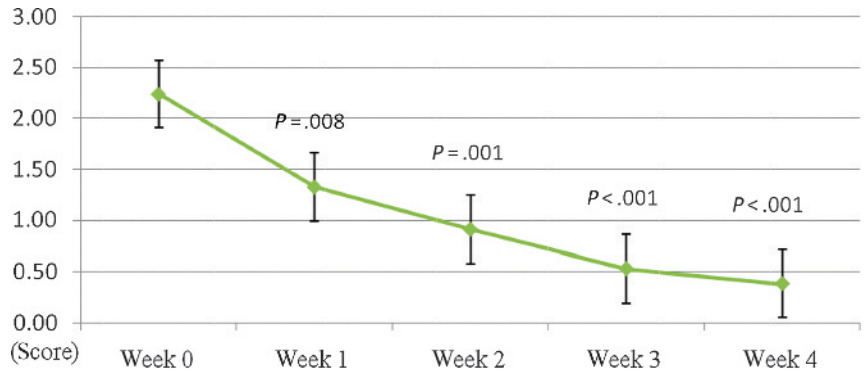


Figure 4.
GENERALIZED ESTIMATING EQUATION MODEL ANALYSIS OF PRURITIS SCALE



use of COL for 1, 2, 3, or 4 weeks as compared with the pretests ($P < .05$). No significant differences, however, were found regarding the impact of demographics and disease characteristics on body surface area affected by dermatologic toxicities ($P > .05$). The body surface area affected decreased from a pretest score of 487.78 ± 135.12 cm^2 (mean ± SE) to a posttest score of 366.97 ± 102.70 cm^2 ($P = .024$) at week 1, 236.30 ± 72.78 cm^2 ($P = .024$) at week 2, 146.62 ± 83.88 cm^2 ($P = .006$) at week 3, and 92.76 ± 80.69 cm^2 ($P = .002$) at week 4 (Figure 3). The results indicated that there were significant differences between pretests and all 4 weekly posttests. The participants' body surface area affected by dermatologic toxicities was significantly reduced in the first week and sustained that reduction over time from the mean pretest score of 487.78 cm^2 to the mean posttest score of 92.76 cm^2 at week 4. Among all the polled participants, 14 (46.67%) had a body surface area of 0 cm^2 at week 4.

In terms of the level of pruritus, the results of the GEE analysis showed significant improvement after continuous use of COL for 1, 2, 3, or 4 weeks as compared with pretests ($P < .001$). There were no significant differences regarding the impact of demographics and disease characteristics on the level of pruritus ($P > .05$). The level of pruritus reduced from a pretest score of 2.24 ± 1.46 (mean ± SE) to a posttest score of 1.32 ± 1.41 ($P = .008$) at week 1, 0.91 ± 1.39 ($P = .001$) at week 2, 0.53 ± 1.36 ($P < .001$) at week 3, and 0.38 ± 1.32 ($P < .001$) at week 4 (Figure 4). The results indicated significant differences between the pretests and all the 4 weekly posttests. The participants' level of pruritus was significantly improved in the first week and declined over time from the mean pretest score of 2.24 to the mean posttest score of 0.38 at week 4, which was almost complete remission.

DISCUSSION

Anti-inflammatory Effect of Colloidal Oatmeal

In this pilot study, the participants' dermatologic toxicity severity score and body surface area affected were significantly reduced in the first week and decreased over the 4 weeks. This finding is similar to a study by Alexandrescu et al,[20] who studied treatment with COL (Aveeno; Johnson & Johnson, New Brunswick, New Jersey) 3 times a day for 7 consecutive days in 10 patients receiving EGFRIs and tyrosine-kinase inhibitors and experiencing dermatologic toxicities. The results showed significant improvement of dermatologic toxicity in a mean of 6.8 days after initiation of COL. However, that study did not measure body surface area, affected by toxicities, so comparisons with the findings in this pilot study could not be made.

Colloidal oatmeal contains oat phenols, β-glucan, flavonoids, ferulic acid, and vitamin E, which can improve anti-inflammatory, calming and soothing, and antioxidant effects and also can alleviate xerosis and redness.[14,15] In addition, colloidal oatmeal can be used to improve the symptoms of EGFRI-induced dermatologic toxicity severity.

The participants in this pilot study received follow-up evaluations for possible adverse effects due to COL during the study period. The results showed there were no adverse events reported, such as skin irritation or pain, in the sample of 30 participants. Some of the participants reported that they felt cool and comfortable in their skin after using COL. This finding is congruent with

the view that colloidal oatmeal is a natural moisturizer and protectant with anti-irritant and soothing effects.[14,16,17]

Antipruritic Effect of Colloidal Oatmeal

The results of a long-term follow-up study in 16 patients showed that 100% of the pooled patients experienced EGFRI-induced xerosis, which likely leads to severe pruritus.[6] To the authors' knowledge, however, no clinical research study has evaluated the effect of COL on EGFRI-induced pruritus. Therefore, in this pilot study, the authors compared the findings only with those from other relevant studies.

The study showed that the participants' pruritus was significantly reduced in the first week and declined over the 4 weeks. These findings are consistent with those found in the following studies.[16–18] Pacifico et al[17] studied the effect of COL once a day for 21 consecutive days on 54 patients on dialysis or patients with skin allergy or dermatitis. The results showed that the level of pruritus (10-cm visual analog scale) was reduced from a mean pretest score of 5.8 to a mean posttest score of 3.2 at week 1 and 1.43 at week 3 ($P < .0001$). A 1-group clinical trial conducted by Nebus et al[16] examined the effect of 3 layers of COL twice a day for consecutive 14 days on 28 adult female patients with chronic pruritus and xerosis on lower limbs. The results showed that pruritus and xerosis were improved on the first day after initiation of COL ($P < .05$) and that sustained significant improvement was detected on the 7th and 14th day. Reynertson et al[18] conducted a blinded study of COL twice a day for consecutive 14 days on 29 healthy females with dry and itchy skin on lower limbs. The results showed that the skin symptoms, such as cracking, scaling, dryness, and roughness, were significantly improved on the first day and were continuously improved on the 7th and 14th day after initiation of COL ($P < .05$).

Colloidal oatmeal contains proteins, polysaccharides, essential fatty acids, and phospholipids that can reinforce the skin's protective and moisture barrier to improve the symptoms of pruritus.[16,17] Pacifico et al[17] also confirmed that the moisture level increased from the mean pretest level of 29.4% (extremely dry) to 45.8% at week 1 and then 54.2% at week 3 ($P < .0001$). The increase in moisture level could significantly improve EGFRI-induced xerosis and pruritus. However, the application frequency of COL in these studies was once daily[16] and twice daily,[17,18] respectively, which is different from the frequency (3-5 times daily) adopted in the pilot study. Further formal research should explore whether reduced frequency based on the patient's need can have the desired improvement effect on pruritus.

CONCLUSIONS

The results of this pilot study showed that COL can improve the symptoms of dermatologic toxicities in participants receiving EGFRIs. The mean posttest score at week 4 for dermatologic toxicity severity was 1.67, which refers to all crusted rash without xerosis, redness, or rash; the mean posttest score at week 4 for pruritus was 0.38; 46.67% of the participants had a body surface area of 0 cm^2. These findings indicate that the dermatologic toxicities of the participants receiving EGFRIs had reached complete remission after 4 weeks of COL treatment. Colloidal oatmeal lotion derived from natural plants had fewer potential adverse effects and a lower market price (approximately US $17.6/240-mL bottle) than corticosteroid or antibiotic ointment, which makes COL more suitable for long-term use in participants treated with EGFRIs.

Considering the lack of studies regarding the improvement effect of COL on EGFRI-induced dermatologic toxicities, this study was conducted to test the effects of COL intervention. The generalizability of the study findings is limited, however, because the study used a small sample size and did not include a control group. Similarly, because of the limited financial resources and that the pilot study did not compare objective measures, such as moisture level, pH values, and distribution density of skin signs, the conclusion of this study is limited.

Based on the findings of this study, it is suggested that the use of COL 3 to 5 times a day for only 1 week could significantly reduce the symptoms of dermatologic toxicities in participants treated with EGFRIs. No significant differences were found between subgroups by age, sex, primary tumor site, type of EGFRI, and number of areas affected by dermatologic toxicities. The findings could serve as a reference for further formal study. Future research should adopt 2-group randomized controlled trials with large sample size, include objective measures, and compare the effect of different application frequency of COL to efficiently determine the improvement effect of COL on EGFRI-induced dermatologic toxicities, thereby serving as a reference for clinical practice. ●

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