RESEARCH ARTICLE

Topical Use of Recombinant Human Epidermal Growth Factor (EGF)-Based Cream to Prevent Radiation Dermatitis in Breast Cancer Patients: a Single-Blind Randomized Preliminary Study

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Abstract

Background: The purpose of this study was to assess the effectiveness of a recombinant human epidermal growth factor (EGF)-based cream for the prevention of acute radiation dermatitis in breast cancer patients receiving radiotherapy (RT). Materials and Methods: Between December 2012 and April 2013, 40 breast cancer patients who received postoperative RT were prospectively enrolled in this study and randomly assigned to receive human recombinant EGF-based cream (intervention group) or general supportive skin care (control group). The grade of radiation dermatitis and pain score were examined at weekly intervals during RT and 6 weeks after RT completion. Results: All patients completed the planned RT and complied well with instructions for applying the study cream and general supportive skin care. In the intervention group, radiation dermatitis of maximum grade 3, 2, and 1 developed in 3 (15%), 11 (55%), and 6 patients (30%), respectively. In comparison, in the control group, radiation dermatitis of maximum grade 3, 2, and 1 developed in 8 (40%), 10 (50%), and 2 patients (10%), respectively. The intervention group showed lower incidence of grade 3 radiation dermatitis than the control group (p=0.068 in univariate analysis and p=0.035 in multivariate analysis). There was no statistically significant difference in the maximal pain score between the two groups (p=0.934). Conclusions: This single-blind randomized preliminary study showed that recombinant human EGF-based cream can have a beneficial role in preventing or minimizing radiation dermatitis in breast cancer patients. To confirm the results of our study, additional studies with a large sample size are required.

Keywords: Breast cancer - radiation dermatitis - epidermal growth factor

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Introduction

Because of the proximity of the skin and the tumor, skin toxicity is the most common acute adverse effect of radiotherapy (RT) in breast cancer. Most patients who are treated with RT for breast cancer develop some degree of radiation dermatitis, ranging from mild or brisk erythema to severe moist desquamation (Harper et al., 2004), and severe reactions can impair the quality of life due to pain and lead to interruption of treatment that may be prejudicial to local control (Duncan et al., 1996, Hymes et al., 2006, Pourhoseingholi et al., 2008, Ogce et al., 2013).

Several clinical studies have been carried out to assess the efficacy of various topical interventions in preventing or minimizing radiation dermatitis in breast cancer patients. However, the results have been contradictory and only few topical interventions have shown significant differences in acute radiation dermatitis when comparing different skin care protocols in randomized studies, therefore, to date no standard treatment has been established for the prevention or management of radiation dermatitis (Fisher et al., 2000, Schmuth et al., 2002, Pommier et al., 2004, McQuestion, 2006, Pinnix et al., 2012, Graham et al., 2013).

In Korea, a recombinant human epidermal growth factor (EGF)-based cream (Easydew CR®, DaeWoong Pharm., Seoul, Republic of Korea) has been used to minimize radiation dermatitis. Easydew CR® contains 0.005% recombinant human EGF, which is biologically identical to human EGF. The purpose of this study was to assess the effectiveness of recombinant human EGF-based cream for the prevention of acute radiation dermatitis in breast cancer patients who receive RT.

Materials and Methods

Eligibility criteria for this study were confirmed diagnosis of unilateral breast cancer, no tumor invasion of skin, completion of breast conserving surgery (BCS) with or without adjuvant chemotherapy, planned course of RT to the breast with a minimum dose of 45 Gy, no use of bolus, no concurrent chemotherapy, no history of prior RT to the chest wall, no history of connective tissue disorder such as systemic lupus erythematosus or scleroderma, and no rashes or unhealed wounds in the radiation field.

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Institutional Review Board approval was obtained for this study and written consent was obtained from all patients.

Between December 2012 and April 2013, 40 patients were prospectively enrolled in this study and randomly assigned to receive human recombinant EGF-based cream or general supportive skin care. Because body mass index (BMI) is a known risk factor influencing the severity of radiation dermatitis (Fernando et al., 1996; Wells et al., 2004), the randomization was stratified according to BMI (<25 kg/m^2 vs. ≥25 kg/m^2) and was generated by computer. The patients who were assigned to receive human recombinant EGF-based cream (intervention group) were instructed to apply the study cream on the irradiated area three times daily. Application was started at onset of RT until 2 weeks after completion of RT or until radiation dermatitis subsided. The assigned study cream was not applied within 4 hours of the daily RT session and patients were instructed to clean the cream from the irradiated area gently with water and a soft towel before the start of daily RT. In the case of an adverse reaction to the study cream, applications were ceased. No other prophylactic creams or lotions were allowed. The patients who were assigned to general supportive skin care (control group) were instructed to keep the irradiated skin clean and dry by gentle washing with or without mild soap and patting with soft towel, and not to use cosmetics or perfume on the irradiated area. No prophylactic creams or lotions were allowed. Compliance with instructions for applying the study cream and general supportive skin care was evaluated weekly by the treating physician.

RT was delivered using a photon beam to the whole breast. With a schedule of 2 Gy per fraction and five fractions weekly, the whole breast was treated with tangential fields to 46-50 Gy. In patients with risk factors for local recurrence (lymphovascular invasion, close margin, or positive axillary lymph nodes), an electron boost to the tumor bed with an additional dose of 10-16 Gy was implemented. Infra- or supra-clavicular lymph nodal irradiation was also delivered to patients with risk factors for regional recurrence (lymphovascular invasion, positive axillary lymph nodes, or extranodal extension), with a total dose of 50-60 Gy. Bolus was not used in any of the patients.

In all patients, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) status were recorded. Patients were classified according to receptor status: luminal (ER- or PR-positive), triple negative (ER-, PR-, HER2-negative), and HER2-positive (ER-, PR-negative, and HER2-positive).

Patients were examined at baseline, and at weekly intervals during RT and 6 weeks after its completion. Skin toxicity was scored according to the Radiation Therapy Oncology Group (RTOG) criteria by a radiation oncologist who was blinded to the groups the patients were assigned to. The patients' evaluation of pain within the RT field was assessed with a 10-cm visual analog scale (VAS). At the end of the study, patients in the intervention group were asked to complete a simple questionnaire to assess their satisfaction with respect to ease of application.

The primary endpoint was the maximum grade of radiation dermatitis developed during RT and the follow-up period. The secondary endpoint was maximum pain score. Baseline characteristics of the two groups of patients were compared by independent t-test or chi-square test. To assess the differences in the maximum grade of radiation dermatitis between the two groups, we compared the actuarial rate of radiation dermatitis estimated using the Kaplan-Meier method, and comparison among groups was performed using the log-rank test. Elapsed time was calculated from the date of initiation of RT to the date of occurrence of maximum radiation dermatitis or final follow-up visit. Maximum pain score between two groups was compared by independent t-test. Parameters evaluated as potential prognostic factors for radiation dermatitis were age, total RT dose, lymph nodal irradiation, BMI, breast size, cancer molecular subtypes, adjuvant chemotherapy, diabetes mellitus, and recombinant human EGF-based cream. All parameters were categorized into two groups according to distribution. The Cox proportional hazard regression model was used for multivariate analysis. All tests were two-sided and $p<0.05$ was considered statistically significant. All analyses were performed using SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA).

Results

All patients completed the planned RT and complied well with instructions for applying the study cream and general supportive skin care. All patients were evaluated for the grade of radiation dermatitis and pain score according to the planned follow-up schedule. Only one patient in the intervention group applied the study cream less frequently (twice daily) for 4 days. As we did not exclude this patient from the study, all patients were evaluable.

Patient characteristics are summarized in Table 1. No statistically significant difference was found between intervention and control groups. All patients were followed-up until 6 weeks after completion of RT. The median follow-up period for all patients was 13.6 weeks (range, 12.6-14.6 weeks). No patient experienced RT interruption.

In the total patient population, 11 patients (27.5%) experienced radiation dermatitis of maximum grade 3, 21 (52.5%) experienced maximum grade 2, and 8 (20%) experienced maximum grade 1. All patients experienced grade 1 or higher radiation dermatitis. In the intervention group, radiation dermatitis of maximum grade 3, 2, and 1 developed in 3 (15%), 11 (55%), and 6 patients (30%), respectively. In comparison, in the control group, radiation dermatitis of maximum grade 3, 2, and 1 developed in 8 (40%), 10 (50%), and 2 patients (10%), respectively (Table 2). The intervention group showed lower incidence of grade 3 radiation dermatitis than the control group ($p=0.068$) (Figure 1A).

In the total patient population, the mean maximal pain score evaluated on the VAS was 3.13 (range, 0-7; standard deviation, ±1.64). The mean maximal pain score in the intervention group and control group was 2.80 (range, 0-6; standard deviation, ±1.67) and 3.13 (range, 0-7; standard deviation, ±1.61). There was no statistically significant difference in the maximal pain score between the two

Table 1. Patient Charateristics

		Intervention group (Recombinant human EGF-based cream) (n=20)	Control group (General supportive skin care) (n=20)	p value
Age (years): Median (range)		57.3 (40.2-74.0)	51.8 (36.5-76.1)	0.553
Total RT dose (Gy): Median (range)		56 (46-66)	56 (46-60)	0.698
Lymph node irradiation				
	Yes	5 (25%)	3 (15%)	0.429
	No	15 (75%)	17 (85%)	
Body mass index (kg/m^2): Median (range)		23.3 (19.6-32.9)	23.6 (17.8-38.3)	0.625
Breast size* (cc): Median (range)		488.8 (209.9-1142.7)	482.1 (228.4-1626.1)	0.911
Molecular subtypes				
	Luminal	16 (80%)	16 (80%)	0.861
	Triple negative	3 (15%)	2 (10%)	
	HER2-positive	1 (5%)	2 (10%)	
Adjuvant chemotherapy				
	Yes	10 (50%)	9 (45%)	0.923
	No	10 (50%)	11 (55%)	
Diabetes mellitus	Yes	2 (10%)	3 (15%)	0.635
	No	18 (90%)	17 (85%)	
Smoking history				
	Current smoker	1 (5%)	0	0.753
	Never smoker	17 (85%)	18 (90%)	
	Quit ≥6 months	2 (10%)	2 (10%)	
T stage	1	12 (60%)	14 (70%)	0.476
	2	7 (35%)	5 (25%)	
	3	1 (5%)	1 (5%)	
N stage	0	16 (80%)	16 (80%)	0.394
	1	1 (5%)	3 (15%)	
	2	2 (10%)	1 (5%)	
	3	1 (5%)	0	

*Breast size calculated by clinical target volume (CTV) of whole breast in radiotherapy planning computer; EGF, epidermal growth factor; RT, radiotherapy; HER2, human epidermal growth factor receptor-2

Table 2. Maximum Radiation Dermatitis During Radiotherapy in Intervention and Control Groups

RTOG toxicity grade	Intervention group (Recombinant human EGF-based cream) (n=20)	Control group (General supportive skin care) (n=20)
1	6 (30%)	2 (10%)
2	11 (55%)	10 (50%)
3	3 (15%)	8 (40%)

*RTOG, Radiation Therapy Oncology Group; EGF, epidermal growth factor

groups (p=0.934).

Prognostic factors for grade 3 radiation dermatitis were analyzed for all patients. In univariate analysis, factors associated with grade 3 radiation dermatitis were total RT dose (p=0.041) and lymph nodal irradiation (p=0.016). In multivariate analysis, lymph nodal irradiation (hazard ratio, 5.308; 95% confidence interval, 1.571-17.934; p=0.025) remained a significant prognostic factor for grade 3 radiation dermatitis, and application of human recombinant EGF-based cream also showed a significant association with grade 3 radiation dermatitis (hazard ratio, 0.232; 95% confidence interval, 0.060-0.903; p=0.035) (Figure 1 and Table 3).

All patients in the intervention group completed a self-administered questionnaire for assessment of their satisfaction with respect to ease of treatment application. Application of recombinant human EGF-based cream on the irradiated area was considered uncomfortable by nine

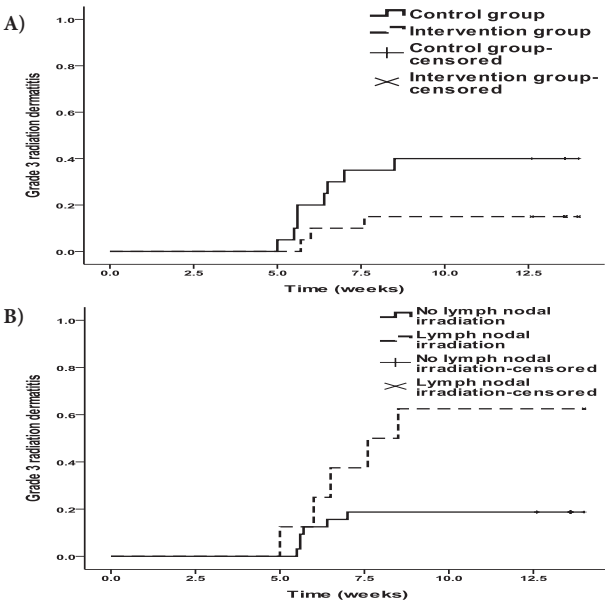

Figure 1. Incidence of Grade 3 Radiation Dermatitis According to. A) Skin Care Protocols, the patients who were assigned to receive human recombinant epidermal growth factor (EGF)-based cream (intervention group) showed lower incidence of grade 3 radiation dermatitis than the patients who were assigned to general supportive skin care (control group) (p=0.068). In multivariate analysis, a statistically significant difference between the two groups was found for the incidence of grade 3 radiation dermatitis (hazard ratio, 0.232; 95% confidence interval, 0.060-0.903; p=0.035). **B)** Lymph Nodal Irradiation, the patients who received lymph nodal irradiation showed higher incidence of grade 3 radiation dermatitis than the patients who did not receive lymph nodal irradiation (p=0.016). In multivariate analysis, a statistically significant difference between the two groups remained (hazard ratio, 5.308; 95% confidence interval, 1.571-17.934; p=0.025)

Table 3. Analysis of Prognostic Factors for Grade 3 Radiation Dermatitis

Variables	Crude incidence rate of grade 3 radiation dermatitis (%)	p value Univariate analysis	p value Multivariate analysis
Age (years): ≤50 vs. >50	40.0 vs. 20.0	0.154	0.432
Total RT dose (Gy): ≤56 vs. >56	19.4 vs. 55.6	0.041	0.544
Lymph node irradiation: Yes vs. No	62.5 vs. 18.8	0.016	0.025
Body mass index (kg/m^2): <25 vs. ≥25	15.4 vs. 33.3	0.259	0.514
Breast size* (cc): <500 vs. ≥500	26.1 vs. 29.4	0.674	0.259
Molecular subtypes: Luminal vs. TN or HER2-positive	25.0 vs. 37.5	0.362	0.215
Adjuvant chemotherapy: Yes vs. No	36.8 vs. 19.0	0.263	0.917
Diabetes mellitus: Yes vs. No	60.0 vs. 22.9	0.089	0.065
Recombinant human EGF-based cream: Yes vs. no	15.0 vs. 40.0	0.068	0.035

*Breast size calculated by clinical target volume (CTV) of whole breast in radiotherapy planning computer; RT, radiotherapy; TN, triple negative; HER2, human epidermal growth factor receptor-2; EGF, epidermal growth factor

patients (45%). The main reason for this discomfort was a feeling of wetness.

No allergic reactions were observed or reported in patients who applied recombinant human EGF-based cream.

Discussion

Numerous studies using different compounds such as corticosteroid, aloe vera, hyaluronic acid, sucralfate, biafine, moisturizing durable barrier cream, ascorbic acid, silver sulfadiazine, and calendula have been performed to identify a topical agent that prevents or minimizes the acute radiation dermatitis, but the results of most studies were negative or contradictory (Halperin et al., 1993, Williams et al., 1996, Fisher et al., 2000, Bostrom et al., 2001, Schmuth et al., 2002, Pommier et al., 2004, Merchant et al., 2007, Kirova et al., 2011, Hemati et al., 2012, Pinnix et al., 2012, Graham et al., 2013). A few topical agents demonstrated a superior efficacy in preventing acute radiation dermatitis in randomized phase III trials (Schmuth et al., 2002, Pommier et al., 2004), however, there is no general agreement on the gold-standard approach for prevention or minimization of acute radiation dermatitis, and clinical practice seems to be varied across countries and institutions.

In Korea, a recombinant human EGF-based cream (Easydew CR®) has been used to minimize radiation dermatitis in clinical practice. Easydew CR® contains highly purified recombinant human EGF (which contains complete 53 amino acid residues and is biologically identical to human EGF), ceramide, hyaluronic acid, Inca omega oil, Portulaca oleracea extract, mango butter, and Meadowform oil. EGF was discovered in the mouse salivary gland in 1962 and interacts with the EGF receptor on epidermal cells and fibroblasts (Cohen, 1962; Nanney, 1990). The healing process of radiation-induced skin damage is not yet fully understood, but epidermal regeneration, fibroblast proliferation, and collagen deposition are known to be important steps in the process (Olascoaga et al., 2008). EGF has been reported to significantly accelerate epidermal regeneration (Brown et al., 1986), and to stimulate the proliferation of fibroblasts that actively synthesize collagen during the wound healing process (Dormand et al., 2005; Ryu et al., 2010). Therefore, topical treatment with EGF may accelerate healing of radiation-induced skin damage.

Several studies have been reported the efficacy of topical treatment with EGF for wound healing in human and animal models. Brown et al. (1989) and Hong et al. (2006b; 2008) reported that topical EGF accelerates the wound healing time, and Tsang et al. (2003) and Hong et al. (2006a) also showed that topical treatment with EGF has positive effects in promoting the healing of chronic diabetic foot wounds in patients with diabetes. EGF has been reported to enhance radiation-induced skin or mucosal damage repair in animal models (Lee et al., 2007a; 2008; Ryu et al., 2010), and Lee et al. (2007b) reported that topical EGF stimulates epithelialization of a chronic radiation-induced ulcer in a breast cancer patient. In our preliminary study, we found that topical use of EGF-based cream can have a beneficial role in the prevention of grade 3 radiation dermatitis in patients undergoing RT for breast cancer.

The reported incidence of radiation dermatitis after breast irradiation has varied widely. In patients who applied topical agents such as hyaluronic acid, calendula, trolamine, silver sulfadiazine, and moisturizing durable barrier cream, the reported rates of maximum grade 4, 3, 2, and 1 radiation dermatitis were ranged 0-2%, 0-35%, 41-63%, and 2-50%, respectively. In patients who received general supportive skin care, the reported rates of maximum grade 4, 3, 2, and 1 radiation dermatitis were ranged 0-2%, 3-53%, 32-63%, and 6-58%, respectively (Fisher et al., 2000; Fenig et al., 2001; Pommier et al., 2004; Leonardi et al., 2008; Hemati et al., 2012; Pinnix et al., 2012; Graham et al., 2013). In our study, maximum grade 4 radiation dermatitis did not develop. In the intervention group, maximum grade 3, 2, and 1 radiation dermatitis developed in 15%, 55%, and 30% of patients, respectively, compared with 40%, 50%, and 10% of cases in the control group. Inconsistencies in the reported rate of radiation dermatitis may be mainly attributable to subjectivity in the scoring criteria for radiation dermatitis. Because most of the scoring criteria for radiation toxicities are based on evaluation by the treating physicians, inter- and intra-observer variation may be present. Other possible reasons for inconsistencies in the reported rate of radiation dermatitis include different indications and regimens of adjuvant chemotherapy, various RT dose fractionation schedules, and heterogeneous patient populations.

Several prognostic factors for radiation-induced skin toxicity have been proposed. Treatment-related factors include total RT dose, RT fraction size, RT technique, volume of skin irradiated, and addition of adjuvant chemotherapy. Patient-related factors include breast size, smoking history, diabetes mellitus, and BMI (Tucker et al., 1992; Fernando et al., 1996; Fisher et al., 2000; Pommier et al., 2004; Xie et al., 2012). In our study, total RT dose and lymph nodal irradiation were significant prognostic factors for radiation dermatitis. Because lymph nodal irradiation represents the volume of skin irradiated, the results of our study support the role of total RT dose and volume of skin irradiated as predictors for the severity of radiation dermatitis. Because of the small sample size, we could not find a significant association between patient-related factors and radiation dermatitis in our study.

Although we did not perform a double-blind randomized study, the grade of radiation dermatitis was scored by a well-trained radiation oncologist who was blinded to the groups the patients were assigned to. Because patients in the intervention group were instructed not to apply study cream within 4 hours of each daily RT session and to clean the study cream from the irradiated area with water and a soft towel before starting the daily RT treatment, we could maintain blindness of the radiation oncologist who scored the grade of radiation dermatitis. In addition, to assess differences in the maximum grade of radiation dermatitis between the two groups, we compared the actuarial incidence rate of radiation dermatitis rather than the crude incidence rate. Because the onset time of radiation dermatitis is as important as the occurrence, we believe that comparing actuarial rate of radiation dermatitis is reasonable.

There were some limitations in this study. First, this is a preliminary study with a small sample size. Therefore, this study lacks sufficient data to make conclusions on the efficacy of recombinant human EGF-based cream.

Second, we could not analyze some potential prognostic factors for radiation dermatitis, such as patient skin type and smoking history. Third, because the patients were not blinded to their group assignment, their evaluation of pain score might be over- or under-estimated. Despite these limitations, we believe that our study contributes to the development of new products for the prevention of radiation dermatitis in breast cancer patients who receive RT.

In conclusion, this single-blind randomized preliminary study showed that recombinant human EGF-based cream can have a beneficial role in preventing or minimizing radiation dermatitis in breast cancer patients. To confirm the results of our study, additional studies with a large sample size are required.

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