

Randomized double-blind trial of prophylactic topical Evozac[®] Calming Skin Spray for gefitinib-associated acne-like eruption

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Background: “Gefitinib” is a first-generation epidermal growth factor receptor tyrosine-kinase inhibitor. More than half of patients receiving gefitinib develop acne-like eruption. Evozac[®] Calming Skin Spray (Evaux Laboratoires, Évaux-les-Bains, France) is made of Évaux thermal spring water and commonly used for the treatment of dermatological toxicities caused by anti-epidermal growth factor receptor therapy. The aim of the study reported here was to test the effect of Evozac Calming Skin Spray on the prevention of rash in patients receiving gefitinib.

Methods: Non-small-cell lung cancer patients preparing to initiate gefitinib therapy were randomly assigned to apply Evozac Calming Skin Spray or physiological saline to the face three times a day. The treatment was started on the same day as initiation of gefitinib therapy and continued for 4 weeks.

Results: A total of 51 patients in the Evozac Calming Skin Spray group and 50 patients in the physiological saline group completed the study per the protocol. The number of facial lesions peaked at the end of 3 weeks in both groups. There were significantly fewer lesions in the Evozac Calming Skin Spray group than in the physiological saline group at the end of 1 week (0.25 versus [vs] 1.10, $P=0.031$) and 3 weeks (6.67 vs 12.26, $P=0.022$). Patients from the Evozac Calming Skin Spray group also developed fewer facial lesions at the end of 2 weeks and 4 weeks, however, the difference was not statistically significant. At the end of 4 weeks, fewer patients from the Evozac Calming Skin Spray group developed rash of grade 2 or greater severity (17.6% vs 36.0%, $P=0.037$), or experienced rash-associated symptoms (13.7% vs 34.0%, $P=0.017$).

Conclusion: Prophylactic treatment with Evozac Calming Skin Spray appears to decrease the number of facial lesions at the peak of the rash, reduce the incidence of grade 2 or more severe rash and relieve rash-associated symptoms.

Keywords: dermatological toxicities, facial rash lesions, rash severity, rash-associated symptoms

Introduction

Epidermal growth factor receptor (EGFR) has been well established as an important target for the treatment of several tumors, including lung, head and neck, colorectal, breast, and pancreatic cancer.¹ EGFR can be inhibited by monoclonal antibodies generated against the ligand-binding domain of the receptor or small-molecule tyrosine kinase inhibitors (TKIs) that compete with the intracellular adenosine triphosphate binding domain of the receptor.²

Dermatologic toxic effects are the major side effects associated with EGFR inhibition. Common dermatological side effects include acneiform skin rash, pruritus, mucositis, xerosis, fissures, hyperpigmentation, nail changes, hair loss, and changes in colour.³⁻⁵ Incidences of these side effects range from 50% to 90%, and side effects

of grade 3 or greater severity occur in 3% to 20% of patients receiving EGFR inhibition.^{6–13} Although a systematic review including 8,998 cancer patients receiving an EGFR inhibitor concluded that there were no reported deaths from dermatologic toxicities,¹⁴ the skin side effects could lead to dose modification or discontinuation of the treatment, and adversely affect patients' quality of life.^{15–18}

"Gefitinib" is a first-generation reversible EGFR-TKI widely used in the treatment of non-small-cell lung cancer (NSCLC) patients with EGFR mutations. More than half of patients receiving gefitinib develop dermatological side effects. Evozac[®] Calming Skin Spray (Evaux Laboratories, Évaux-les-Bains, France) is made of Évaux thermal spring water, which is naturally rich in lithium. It is commonly used to manage dermatological toxicities caused by chemotherapy, radiation therapy, and anti-EGFR therapy in several countries. It has been reported that Evozac Calming Skin Spray can relieve the dermatological toxicities of patients under anti-EGFR therapy.¹⁹ However, to the best of our knowledge, there has been no formal clinical trial designed to examine the role of Evozac Calming Skin Spray in managing skin side effects induced by EGFR inhibitors. Thus, the present trial was conducted to test the effect of Evozac Calming Skin Spray in the prevention of rash in patients receiving gefitinib (NCT01528488).

Patients and methods

The study was designed as a single-center, randomized, double-blind, placebo-controlled trial, and approved by the institutional review board of Sun Yat-sen University Cancer Center. Informed consent was obtained from each participant.

Patient eligibility

Patients who met the following criteria were eligible to enroll in the study: ≥ 18 years old, histologically confirmed diagnosis of NSCLC, preparing to initiate gefitinib treatment, and normal hepatic and renal function. Study exclusion criteria were: Eastern Cooperative Oncology Group score ≥ 3 ; pregnancy; use of therapies within 4 weeks prior to enrollment that may induce similar skin reaction, such as cetuximab or sorafenib; use of anti-inflammatory or antibiotic drugs for other conditions; or any rash at the time of study registration.

Treatment

Eligible patients were randomly assigned to apply Evozac Calming Skin Spray or physiological saline. The topical

treatment was started on the same day as initiation of gefitinib therapy and continued for 4 weeks. Patients were instructed to apply the Evozac Calming Skin Spray or physiological saline to the face three times a day, in the morning, at noon, and at bedtime. Patients were asked to record use of the study treatment, as well as that of gefitinib, in a study diary.

Evaluation

At baseline, a clinical history was obtained for all participants and a physical examination performed. Patients' Eastern Cooperative Oncology Group performance score within 1 week of trial registration was also assessed. A blood draw for assessment of serum creatinine and total bilirubin levels was obtained. Finally, patients also underwent a complete skin examination by the participating oncologists, as well as standardized digital photography of the face.

The total number of patient face lesions was calculated at the end of Week 1, 2, 3, and 4. At the end of 4 weeks, each patient's treating oncologist was to perform an evaluation, which included taking a history and performing a physical examination; an assessment of patient performance status; an assessment of rash-associated symptoms (itching, dry skin, pain, and irritation); and an assessment of rash severity, per the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). In addition, digital photography utilizing the same standard poses as at baseline was also performed at Week 4. Further, because some preliminary studies indicated that the plasma concentration of gefitinib might be associated with the severity of the skin side effects, the plasma concentration of gefitinib was tested at Week 4. Plasma samples (2 mL) of the participants were collected on Day 28 and frozen at -80°C until required for analysis. The steady-state trough concentration was analyzed using a validated high-performance liquid chromatographic method with tandem mass spectrometry.

Statistical analysis

The primary endpoint was difference in total number of face lesions between Evozac Calming Skin Spray- and physiological saline-treated patients at completion of the study period (Week 4). Secondary endpoints were differences in total number of face lesions between Evozac Calming Skin Spray- and physiological saline-treated patients at the other follow-up intervals (Weeks 1–3), difference in rash severity evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (v 3.0) between the two arms at Week 4, and difference in rash-associated symptoms between the two arms at Week 4.

A sample size of 48 patients per group provided a 90% probability of detecting a lesion count difference of four between the two study arms and of thereby rejecting the null hypothesis of equal proportions with a P -value of 0.05 as a two-sided test. Assuming the dropout rate of <20%, it was determined that 59 patients should be enrolled in each arm. SPSS for Windows software (v 19.0; IBM Corporation, Armonk, NY, USA) was used for all data analysis. The normality of quantitative variables was analyzed using the Shapiro–Wilk test. Quantitative variables according with normal distribution were analyzed by independent-sample t -test; Quantitative variables departing from the normal distribution were analyzed using the Mann–Whitney U test. Pearson's chi-squared test and Fisher's exact test were used to test the difference in the distribution of categorical variables when appropriate. All significance levels reported refer to two-sided tests. A P -value of <0.05 was considered significant.

Results

Between December 2011 and July 2013, 118 NSCLC patients were randomly assigned to the Evozac Calming Skin Spray group ($n=59$) or physiological saline group ($n=59$) on the same day of initiation of gefitinib treatment. Details of

patient attrition during the study are shown in Figure 1. In total, 51 patients in the Evozac Calming Skin Spray group and 50 patients in the physiological saline group completed the study per protocol; the baseline characteristics of these patients are listed in Table 1. There was no significant difference in the baseline characteristics between the two arms.

As shown in Figure 2, the number of lesions increased rapidly over the first 3 weeks of the study then began to decrease. Table 2 lists the total number of patient face lesions at the end of Weeks 1, 2, 3, and 4. At the end of Week 1 and Week 3, the total number of facial lesions in the Evozac Calming Skin Spray group was significantly fewer than that of the physiological saline group. Patients in the Evozac Calming Skin Spray group also developed fewer facial lesions compared with patients in the physiological saline group at the end of Week 2 and Week 4. However, the difference was not statistically significant.

With regard to rash severity, in the Evozac Calming Skin Spray group, 21 patients were diagnosed with grade 1 rash, eight with grade 2 rash, and one with grade 3 rash at the end of 4 weeks, while, in the physiological saline group, 18 patients were diagnosed with grade 1 rash, 16 with grade 2 rash, and two with grade 3 rash. In total, rash of grade 2 or greater severity occurred in 17.6% (9/51) of the Evozac

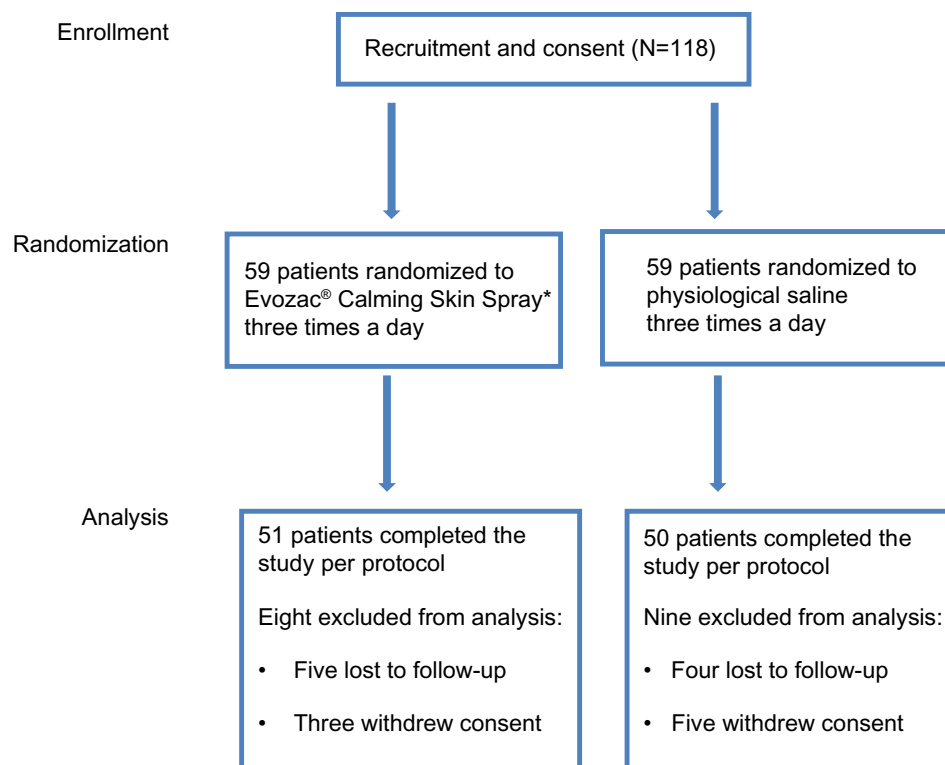


Figure 1 Study enrollment, randomization, and attrition data.

Note: *Evaux Laboratories, Évaux-les-Bains, France.

Table 1 Baseline characteristics of the patients

Characteristic	Evozac® Calming Skin Spray* arm (n=51)		Physiological saline arm (n=50)		P-value
	N	%	N	%	
	Sex				
Male	27	52.9	24	48.0	
Female	24	47.0	26	52.0	
Age, years (mean ± standard deviation)	54.3±10.9		57.7±9.6		0.101
Stage					0.678
IIIB	4	7.8	2	4.0	
IV	47	92.2	48	96.0	
ECOG PS					0.649
0	5	9.8	8	16.0	
1	35	68.6	32	64.0	
2	11	21.6	10	20.0	
EGFR mutation					0.605
19 exon	23	45.1	17	34.0	
21 exon	21	41.2	22	44.0	
Wild-type	6	11.8	9	18.0	
Other	1	1.9	2	4.0	
Histological type					0.565
Adeno	42	82.4	36	72.0	
Adeno-squamous	7	13.7	9	18.0	
Squamous	1	2.0	3	6.0	
Other	1	2.0	2	4.0	
Treatment					0.224
First line	30	58.8	31	62.0	
Maintenance	7	13.7	2	4.0	
Second line	5	9.8	3	6.0	
Third or later line	9	17.6	14	28.0	
Smoking history					0.916
Never smoker	28	54.9	26	52.0	
Ex-smoker	19	37.2	19	38.0	
Current smoker	4	7.8	5	10.0	
Allergy history					0.617
Yes	1	2.0	2	4.0	
No	50	98.0	48	96.0	
Skin-disease history					0.715
Yes	5	9.8	3	6.0	
No	46	90.2	47	94.0	

Note: *Evaux Laboratories, Évaux-les-Bains, France.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; EGFR, epidermal growth factor receptor.

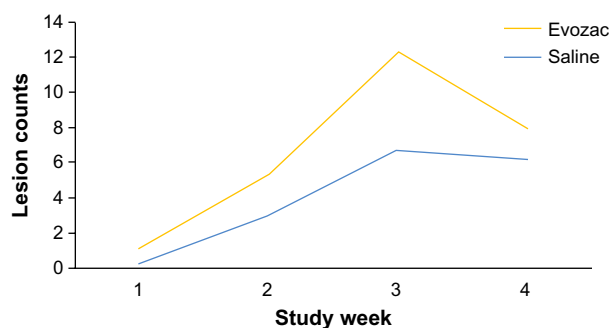


Figure 2 Mean number of facial lesions in Evozac® Calming Skin Spray (Evaux Laboratories, Évaux-les-Bains, France) group and physiological saline group at each of the four study time points.

Table 2 Total number of patient facial lesions

Week	Evozac® Calming Skin Spray**		Saline		P-value*
	Mean	Range	Mean	Range	
	1	0.25	0–4	1.10	
2	2.96	0–21	5.34	0–38	0.088
3	6.67	0–59	12.26	0–80	0.022
4	6.18	0–63	8.02	0–59	0.058

Notes: *Based on Mann–Whitney *U* test of total number of lesions at each study time point; **Evaux Laboratories, Évaux-les-Bains, France.

Calming Skin Spray-treated patients and in 36.0% (18/50) of the physiological saline-exposed patients, and the difference reached statistical significance ($P=0.037$).

In addition, an assessment of rash-associated symptoms (itch, dry skin, pain, and irritation) was performed at the end of Week 4. In the Evozac Calming Skin Spray-treated group and physiological saline-exposed group, 13.7% (7/51) and 34.0% (17/50) of patients experienced one or more rash-associated symptoms, respectively. This difference was of statistical significance ($P=0.017$).

The steady-state trough concentration of gefitinib was available for 43 patients in the Evozac Calming Skin Spray group and 35 patients in the physiological saline group. The concentration was comparable between the Evozac Calming Skin Spray group (mean 172.4, median 159.4, range 47.8–433.0 ng/mL) and the physiological saline group (mean 170.2, median 145.1, range 51.8–391.8 ng/mL) ($P=0.533$).

Discussion

To the best of our knowledge, the trial reported here is the first clinical study to test the effectiveness of Evozac Calming Skin Spray for the management of dermatological toxicities caused by gefitinib. Designed as a randomized, double-blind, placebo-controlled trial, this study sought as its primary endpoint to determine whether Evozac Calming Skin Spray could reduce the number of facial lesions at the end of 4 weeks. Evozac Calming Skin Spray did not appear to decrease the number of facial lesions compared with placebo at the end of 4 weeks.

However, despite the fact that the primary endpoint was not reached, the results of the study have generated some useful findings. Evozac Calming Skin Spray did reduce the total number of facial lesions at the end of Week 1 and 3. Considering that the lesion counts peaked at the end of 3 weeks, Evozac Calming Skin Spray seemed to decrease the number of facial lesions at the peak of the rash. In addition, at the end of 4 weeks, a decrease in the incidence of grade 2 or more severe rashes in patients assigned to the

Evozac Calming Skin Spray arm was noted. Further, fewer patients from the Evozac Calming Skin Spray arm suffered from rash-associated symptoms (itch, dry skin, hurting and irritation) than patients treated with placebo. In view of these points, patients could benefit from treatment with Evozac Calming Skin Spray.

The underlying mechanism responsible for why Evozac Calming Skin Spray can help manage the dermatological toxicities associated with gefitinib remains unclear. One reasonable explanation is that the Evozac Calming Skin Spray contains rich lithium (2.20 mg/L). The pathogenesis of the EGFR-TKI-induced rash involves abnormalities in the follicular epithelium together with inflammation. Lithium may have anti-inflammatory effects on keratinocytes by increasing expression of interleukin 10 and decreasing expression of Toll-like receptors 2 and 4.²⁰ Topical agents containing lithium have been widely used for the treatment of inflammatory dermatitis, especially seborrheic dermatitis, and significantly improve patient symptoms.^{21–24} In addition, activation of the neurokinin-1 receptor by substance P is associated with pruritus and other symptoms of EGFR-TKI-induced rash.²⁵ Lithium could inhibit the effect stimulated by substance P²⁶ and relieve the symptoms of rash.

Our study has some limitations. Since only patients receiving gefitinib were enrolled in the study, the effect of Evozac Calming Skin Spray on dermatological toxicities associated with other EGFR-TKIs or anti-EGFR antibodies is uncertain. Considering that the pathogenesis of skin toxicities during use of anti-EGFR antibodies or TKIs is thought to be similar, Evozac Calming Skin Spray might also be effective for these. However, further trials should be undertaken to validate the efficacy of Evozac Calming Skin Spray for the treatment of dermatological toxicities caused by other EGFR inhibition therapies. In addition, although assessment of rash-associated symptoms was performed at the end of 4 weeks, patient quality of life was not systematically evaluated in the study. Finally, the number of patients enrolled in the study was relatively small, and large-scale trials are needed to confirm the findings in the future.

Conclusion

Prophylactic treatment with Evozac Calming Skin Spray appears to decrease the number of facial lesions at the peak of the rash, reduce the incidence of grade 2 or more severe rash and relieve rash-associated symptoms. Prophylactic Evozac Calming Skin Spray treatment with gefitinib initiation is reasonable.

Disclosure

The study was funded by Evaux Laboratories. The authors report no other conflicts of interest in this work.

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