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The efficacy of clobetasol, dexpanthenol, and fucidic acid in the treatment of cetuximab-induced skin toxicity

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Abstract
Cetuximab (CTX) is a monoclonal antibody against the epidermal growth factor receptor (EGFR). It is used as a monotherapy or in combination with cytotoxic chemotherapy in metastatic colorectal cancer (mCRC). Severe cutaneous reactions are frequent and major causes of discontinuation of CTX treatment. This open-label study evaluated the efficacy of a mixture drug topically applied to skin lesions in patients with mCRC who developed skin toxicity caused by CTX. Twenty patients with mCRC were included in this prospective, single-center, open-labeled trial. The patients had received CTX in addition to chemotherapy and developed grade 2 or 3 skin toxicity and were treated twice daily with an ointment mixture of clobetasol, dexpanthenol, and fucidic acid. The objective response rate was 100%, and no delay, dose reduction or discontinuation of CTX treatment due to skin toxicity were necessary. Skin toxicity relapsed in the following chemotherapy cycles in all patients after discontinuation of the ointment. Repeated administration of the ointment resulted in improvement of skin toxicity and allowed continuation of CTX treatment. This ointment mixture seems to be effective in the treatment of CTX-induced skin toxicity in patients with mCRC.

Keywords: topical treatment, cetuximab-induced skin toxicity, metastatic colorectal cancer

Introduction

Cetuximab (CTX) is a monoclonal antibody against the epidermal growth factor receptor (EGFR). It is used as monotherapy or in combination with cytotoxic chemotherapy and increases both progression-free survival and overall survival in patients with wild-type RAS metastatic colorectal cancer [1].

Cutaneous reactions are well known and the most commonly experienced adverse events during treatment with EGFR inhibitors, appearing in more than half of patients [2]. In addition, severe skin toxicity develops in 20% of patients [3, 4]. Severe reactions such as acne, folliculitis, xerosis cutis, pruritis, erythema, and paronychia are major causes of discontinuation of treatment with EGFR inhibitors, especially with CTX [5, 6]. CTX-induced acne is different from acne induced by other drugs such as corticosteroids, it is accompanied by xerosis, paronychia, telangiectasia, and hair and nail changes [7]. Epidermal growth factor receptor inhibitors cause deterioration of the epidermis and its barrier function, and aberrant proliferation and differentiation of epithelial cells [5,8]. A mahmut infections [10,12]. Furthermore, high levels of chemokine concentration caused by the inhibition of the EGFR leads to epidermal inflammation [13].

Retrospective analyses of EGFR-targeting treatment in different tumor types, including mCRC, head and neck cancer, pancreatic cancer, and non–small-cell lung cancer have shown a correlation between the severity of skin reactions and treatment efficacy [1,3,14–16]. It was revealed that the development of skin rash was significantly associated with reduced risk of death in patients with mCRC who were treated with CTX or panitumumab [17,18].

Topical fucidic acid is commonly used for local skin infections such as folliculitis, and topical dexpanthenol and clobetasol are used for various types of dermatitis. These three drugs are commonly used alone or as combination drugs in the treatment of radiation-induced dermatitis [19].

The objective of our study was to assess the efficacy of this pomade mixture in CTX-induced skin toxicity in patients with mCRC.

Patients and methods

This study was undertaken in the Istanbul University Institute of Oncology. We enrolled twenty consecutive patients with grade ≥ 2 skin toxicity after first-line CTX

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plus 5-Fluorouracil, folinic acid, irinotecan regimen (FOLFIRI). We excluded patients with known sensitivity to one of these topical agents and those who did not give informed consent.

We evaluated the efficacy of a topical application of an ointment consisting of 0.05% clobetasol 17-propionate, 5% dexpanthenol, and 2% fucidic acid in equal weight. All of the subjects applied the ointment mixture on their skin, twice a day, for 1 week. We instructed the patients to avoid using other topical or oral antibiotics, oral corticosteroids, or other skin moisturizers during this treatment. The severity of skin toxicity was graded by an experienced oncologist in accordance with the United States National Cancer Institute-Common Toxicity Criteria version 3.0 (NCI CTCAE v3.0).

We took photographs of the skin reactions with written permission of the patients. We took the photographs prior to- and 1 week after treatment. The patients were instructed to stop using the ointment at the end of the first week. We informed the patients that they could resume use of the mixture ointment throughout the CTX treatment if the skin reactions recurred.

We performed the study in accordance with the Declaration of Helsinki (5th revision, October 2000). All patients signed informed consent forms before enrollment to this study.

Results

We summarized the patient characteristics, details of the treatment, skin toxicity, and response to the ointment mixture treatment after the 1st week in Table 1. The patients had grade 2 or 3 skin toxicities (Figure 1, 2). Eleven patients had grade 3 skin toxicity. Complete response rates in patients with grade 2 and grade 3 skin toxicities were 88 and 45%, respectively. In all of the remaining patients with grade 2 and 3 skin toxicity, the toxicity regressed to grade 1. Thus, the objective response rate was 100%; no delay, dose reduction or discontinuation of CTX treatment due to skin toxicity was necessary. We observed no adverse events related with the use of the topical ointment. Skin toxicity recurred in all patients when patients stopped administering the ointment and therefore they used it throughout the CTX treatment.

Table 1. The features of patients, details of treatment, skin toxicity and response to soap treatment after the 2nd week

No	Gender	Age	Diagnosis	Treatment	Skin toxicity before ointment application	Skin toxicity after ointment application
1	M	35	mCRC	FOLFIRI-CTX	Grade 3	Grade 1
2	F	40	mCRC	FOLFIRI-CTX	Grade 2	Grade 1
3	F	58	mCRC	FOLFIRI-CTX	Grade 3	Grade 1
4	M	60	mCRC	FOLFIRI-CTX	Grade 2	CR
5	M	54	mCRC	FOLFIRI-CTX	Grade 2	CR
6	F	60	mCRC	FOLFIRI-CTX	Grade 3	CR
7	M	35	mCRC	FOLFIRI-CTX	Grade 2	CR
8	F	48	mCRC	FOLFIRI-CTX	Grade 3	Grade 1
9	F	69	mCRC	FOLFIRI-CTX	Grade 2	CR
10	F	72	mCRC	FOLFIRI-CTX	Grade 3	Grade 1
11	M	70	mCRC	FOLFIRI-CTX	Grade 2	CR
12	M	54	mCRC	FOLFIRI-CTX	Grade 3	CR
13	F	58	mCRC	FOLFIRI-CTX	Grade 2	CR
14	M	65	mCRC	FOLFIRI-CTX	Grade 3	CR
15	F	58	mCRC	FOLFIRI-CTX	Grade 3	Grade 1
16	M	68	mCRC	FOLFIRI-CTX	Grade 2	CR
17	F	59	mCRC	FOLFIRI-CTX	Grade 3	CR
18	M	65	mCRC	FOLFIRI-CTX	Grade 2	CR
19	F	70	mCRC	FOLFIRI-CTX	Grade 3	CR
20	M	35	mCRC	FOLFIRI-CTX	Grade 3	Grade 1

M male, F female, mCRC metastatic colorectal cancer, CR complete response

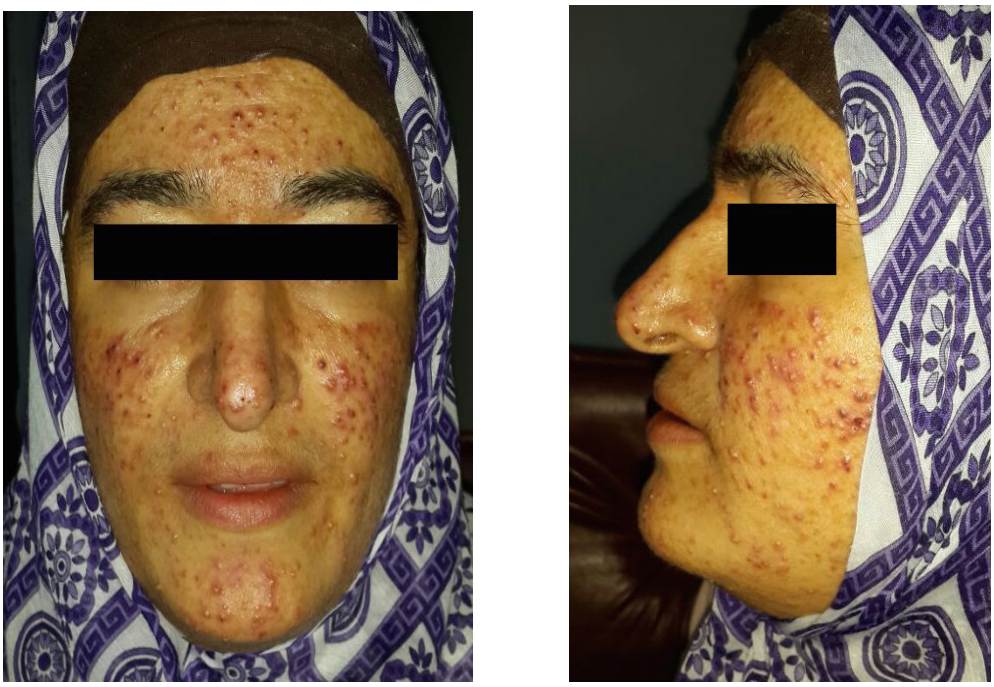

Figure 1. Acneiform eruption. Skin toxicity before using mixture ointment (A: front view, B: side view)

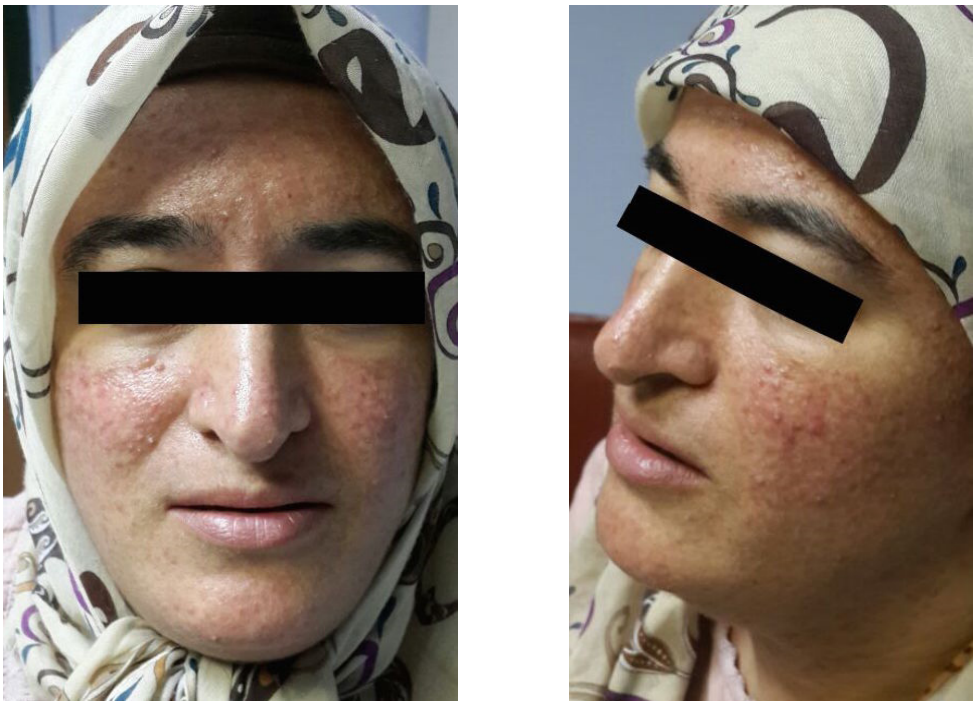

Figure 2. Acneiform eruption. Skin toxicity after using mixture ointment (A: front view, B: side view)

Discussion

In this prospective, open-label study, we observed a favorable response to a topical ointment mixture of clobetasol, dexpanthenol, and fucidic acid in patients with grade 2 or 3 CTX-associated skin toxicity plus FOLFIRI treatment for mCRC. This treatment allowed continuation of the chemotherapy regimen. None of the patients experienced significant adverse events related with the topical ointment.

Quality of life in patients treated with EGFR-targeting agents is adversely impacted because of significant skin toxicity. Grade 3 skin toxicities may entail dose delays or reductions, or even permanent discontinuation of CTX in 10% of patients [10]. The patients at the highest risk for the

development of severe exanthemas are men aged below 70 years receiving concomitant radiotherapy [20].

In a previous study conducted by our institute, we determined the positive effects of Bittim soap (Pistacia terebinthus soap) on CTX-induced skin toxicity in patients with mCRC [21]. As a complement to that previous study, we investigated the efficacy of a mixture of locally-administered ointment of clobetasol, dexpanthenol, and fucidic acid in patients with mCRC who received CTX treatment.

To the best of our knowledge, this is the first study in the literature to investigate the effect of clobetasol, dexpanthenol, and fucidic acid as mixture ointment in the treatment of CTX-induced skin toxicity. In our case series, the ointment mixture completely cured or decreased the grade of grade 2 or 3 skin lesions within 1 week in all patients without adverse effects. A complete response was seen in eight patients with grade 2 skin lesions. One patient's grade 2 skin lesions regressed to grade 1. Of 11 patients with grade 3 skin lesion, 5 showed complete response and grade 3 skin lesions regressed to grade 1 in the remaining 6 patients. However, skin lesions reappeared after cessation of the ointment in all patients.

Other agents used for skin toxicity, pimecrolimus, prophylactic tazarotene, and sunscreen were not successful. Prophylactic oral minocycline reduced the severity of skin toxicity only during the first 2 months of CTX treatment [22-24]. Additionally, prophylactic tetracycline was shown to decrease the intensity of skin toxicity [25]. The Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) trial proved the benefit of prophylactic treatment in patients with mCRC receiving panitumumab, which is another EGFR antagonist. In STEPP, the prophylactic regimen consisting oral doxycycline 100 mg twice daily and a topical steroid (1% hydrocortisone cream) once daily during the first 6 weeks were used during panitumumab-containing chemotherapy regimens. The incidence of grade 2 skin toxicity was lower in patients who received prophylactic treatment even though their chemotherapy doses were higher; consequently, their quality of life was better [26]. Another study that compared prophylactic treatment with the reactive skin treatment concluded that both approaches were equally effective. The remarkable result of this study was that in patients who received neither prophylactic nor reactive skin treatment, the CTX discontinuation rate was 40% [27]. Another non-randomized trial that assessed treatment approaches reported that Regenecare Wound Gel, a mixture of 2 % lidocaine, marine collagen, aloe vera, and sodium alginate, plus nadifloxacin and prednicarbate cream together decreased the severity of skin toxicity and provided relief of symptoms [28,29]. Likewise, in another study, prophylactic cream containing 0.1% vitamin K1 was used and no grade 3 or 4 skin toxicities were experienced [30].

Our study has some limitations. First, there is no control group. Another limitation is that the mixture ointment was not prepared in a standardized manner. However, the responses to the ointment were similar in all patients. This may facilitate the use of this mixture without the aid or need of a pharmacy.

Conclusion

The mixture ointment containing clobetasol, dexpanthenol, and fucidic acid seems to be associated with favorable response in patients with severe skin toxicity associated with CTX plus FOLFIRI treatment in mCRC.

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Ethical standards The study was performed in accordance with the Declaration of Helsinki (5th revision, October 2000) of the World Medical Association. All patients signed informed consent forms.

Conflicts of interest The author declare that she has no conflict of interest.

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