DOI: http://dx.doi.org/10.3315/jdcr.2014.1164

Journal of Dermatological Case Reports

Clinical response of acneiform eruptions caused by cetuximab to administration of oral tetracycline and topical ketoconazole

Satoshi Nakamura[1], *Yoshio Hashimoto*[1], *Kaoru Nishi*[2], *Tosihiro Mizumoto*[1], *Hidetoshi Takahashi*[2], *Hajime Iizuka*[2]

1. Department of Dermatology, Asahikawa Kousei Hospital, Asahikawa, Japan;
2. Department of Dermatology, Asahikawa Medical University, Asahikawa, Japan.

Corresponding author:

Satoshi Nakamura, M.D., PhD.,

Department of Dermatology, Asahikawa Kousei Hospital

1 Joudori 24 Choume 111, Asahikawa, Hokkaido,

Japan, 078-8211

E-mail: *namu@asahikawa-med.ac.jp*

Key words:

acne, adverse event, cetuximab, colon cancer, erlotinib, folliculitis, gefitinib, ketoconazole, panitumumab, tetracycline

Abstract

Background: Cutaneous adverse events associated with the use of epidermal growth factor receptor inhibitors, such as cetuximab are relatively common. Although there are reports about possible treatments for acne or acneiform lesions induced by cetuximab, there are only few reports of prospective studies.

Objective: The aim of the study was to analyze the efficacy of varius treatment modalities and their combinations in patients with acneiform eruptions caused by cetuximab.

Patients and methods: We studied 14 patients treated with an epidermal growth factor receptor inhibitors, including 7 patients cetuximab, who developed acneiform eruptions in the course of therapy. All patients were diagnosed as grade II according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. A corticosteroid ointment, tacrolimus ointment, and ketoconazole ointment were used in a randomized manner. Oral therapy included administration of antihistaminic drugs, tetracycline, a cyclooxygenase inhibitor, or a macrolide. We measured the numer of days required to achieve improvement from grade II to grade I during cetuximab treatment.

Results: Our results showed that tetracycline treatment may shorten the period needed to achieve improvement. Ketoconazole cream and a combination of oral tetracycline and topical ketoconazole also significantly shortened this period.

Conclusion: The results of our short case study may indicate that a combitation therapy of oral tetracyclin and topical ketokonazole is most effective in the therapy of patients with acneiform eruptions caused by cetuximab. (*J Dermatol Case Rep*. 2014; 8(1): 16-19)

Introduction

Recently, many reports have described cutaneous adverse events associated with the use of the epidermal growth factor (EGF) receptor inhibitor cetuximab.[1-2] This may be associated with the fact that the EGF receptor tyrosine kinase, which is over-expressed on cancer cells, also exists in the normal epidermis and normal hair follicles.[3]

EGF receptor inhibitors are classified into 2 classes, i.e., low molecular weight tyrosine kinase inhibitors (gefitinib, erlotinib) and IgG monoclonal antibodies against the EGF receptor (cetuximab, panitumumab). The most common cutaneous adverse effects of the EGFR inhibitors include acneiform lesions (folliculitis), diffuse hair loss, dry skin and paronychia.[1-2]

Folliculitis occurs in 40-85% of patients and is typically observed in the first ten days of treatment. Folliculitis is especially common and often severe with cetuximab. The aim of the study was to analyze the efficacy of varius treatment modalities and their combinations in patients with acneiform eruptions (folliculitis) caused by cetuximab.

Patients and methods

We studied 14 patients, treated with an EGF receptor inhibitors (gefitinib, erlotinib, cetuximab, and panitumumab), including 7 patients who received cetuximab. We selected the treatment in a randomized manner. We evaluated the clinical outcome of various therapies and their combinations.

Grade II acneiform adverse events, caused by cetuximab were diagnosed according to the CTCAE (Common Terminology Criteria for Adverse Events) version 4.0. The characteristics of the patients are summarized in Table 1. All patients had colorectal carcinoma with lymph node involvement, and liver and/or lung metastases. The average period from the appearance of skin lesions was 24.1 days. Five of the 7 patients received oral antihistamine treatment. Three of the 7 patients received oral tetracycline, 1 received an oral macrolide, 2 received a COX2 inhibitor, and 1 received a tacrolimus ointment. Additionally, 4 of the 7 patients used a ketoconazole ointment, and 2 used a corticosteroid ointment during the treatment course. Cetuximab was continuously administered in all cases. The dose was not changed throughout the observation. We compared the subjective itching symptoms by using the visual analogue scale (itching VAS) score. The oral and topical treatment was randomly selected.

We examined skin manifestations and psychosocial impact for several days. We measured the time in which cutaneous conditions improved from grade II to grade I, i.e., the time in which itching, desquamations, and ulcers improved to an extent that the different oral treatments could be discontinued and/or the psychosocial impact was cured.

Patients indicated the degree of itching from maximal to zero by using the blind 10-cm scales and we measured the length.

The duration of grade II events, the itching VAS scores before therapy, and changes in the itching VAS scores were analyzed using the Mann-Whitney U test. All tests were conducted at the 0,05 significance level.

Results

In all patients treated with cetuximab the average itching VAS score significantly decreased from the first (29.3 mm) to the last examination (12.1 mm) ($p < 0.01$) (Table 1). This result demonstrated the effectiveness of all selected therapies analyzed together (Fig. 1A, B and Fig. 1C, D). There were no significant differences between all therapy methods in the itching VAS scores before therapy ($p > 0.05$) (data not shown). This result shows that there was no bias between the different therapies in redard to disease severity. Tetracycline shortened the period of grade II acneiform eruptions (14 days in patients who used tetracycline vs. 47 days in patients who did not use tetracycline; $p < 0.05$) (Table 2). We also found that ketoconazole ointment shortened the period of grade II acneiform rash caused by cetuximab. Interestingly, in the case of ketoconazole ointment (16 days vs. 54 days; $p < 0.05$) or the combination of ketoconazole ointment and tetracycline (14 days vs. 46 days; $p < 0.05$) the difference was also statistically significant. In addition, we evaluated the effect of a COX2 inhibitor on acneiform eruptions. The period of grade II events was significantly longer when a COX2 inhibitor was used compared to when no COX2 inhibitor was used (70 days vs. 17 days; $p < 0.05$).

Discussion

Adverse events, including acneiform eruptions, induced by EGF receptor inhibitors impede a patient's physical and psychological activity. EGF receptors are distributed in cancer cells as well as in the epidermis and hair follicle cells.[3] However, the mechanism oleading to cutaneous adverse events induced by EGF receptor inhibitors remains unknown. Defective or abnormal keratinization may be caused when the EGF receptor is blocked. Furthermore, inflammation of hair follicles may be related to EGF receptor inhibition. Widely recommended therapies for acneiform eruptions caused by EGF receptor inhibitors are systemic tetracycline, topical clindamycin, and topical corticosteroids.[1-2] Some studies have suggested the effectiveness of isotretinoin[4] and colloidal oatmeal lotion.[5] Other authors performed a placebo-controlled trial, which showed that tetracycline was not sufficiently effective against skin rashes induced by the EGF receptor inhibitors gefitinib and cetuximab.[6] We compared the duration of grade II acneiform eruptions caused by various therapies and observed a significant difference in the responses to oral tetracycline administration, ketoconazole ointment, or both in cetuximab-treated patients. As result of our analysis we recommend tetracycline administration and ketoconazole ointment therapy for acneiform eruptions. We hypothesize that the effect of tetracycline and ketoconazole may be related to facial follicular bacteria, which showed an imbalance induced by inflammation, acne folliculitis, or malassezia folliculitis. Furthermore, because of the imbalance of indigenous bacteria, seborrhea-like changes may occur on facial skin.

In our study, treatment with a COX2 inhibitor significantly prolonged the grade II period. Initially, it was shown that UVB exposure and/or EGF receptor signal transduction are related to COX2 expression in HaCaT keratinocytes.[7] Although we expected that a COX2 inhibitor might be effective in reversing the effect on the EGF receptor, the period of grade II events was longer in our study. A recent study showed that the combination of a COX2 inhibitor and an EGF receptor inhibitor resulted in decreased cellular proliferation and increased apoptosis.[8] A further study showed the relationship between rash and life-survival as well as between cetuximab-induced rash and anti-cancer response.[9] These data suggest that the longer period of grade II acneiform eruptions was caused by combined administration of an EGF receptor inhibitor and a COX2 inhibitor. This combination may decrease cellular proliferation and may increase apoptosis of cancer cells as well as keratinocytes and hair follicle cells. The underlying mechanism of this response might involve signal transduction pathways in cancer cells, keratinocytes, and follicular cells. The combination of a COX2 inhibitor and cetuximab might result in synergistic damage to cancer, skin, and follicular cells.

In conclusion, the results of our short study may indicate that a combination of systemic tetracycline and topical ketoconazole is most effective for acneiform eruptions caused by cetuximab.

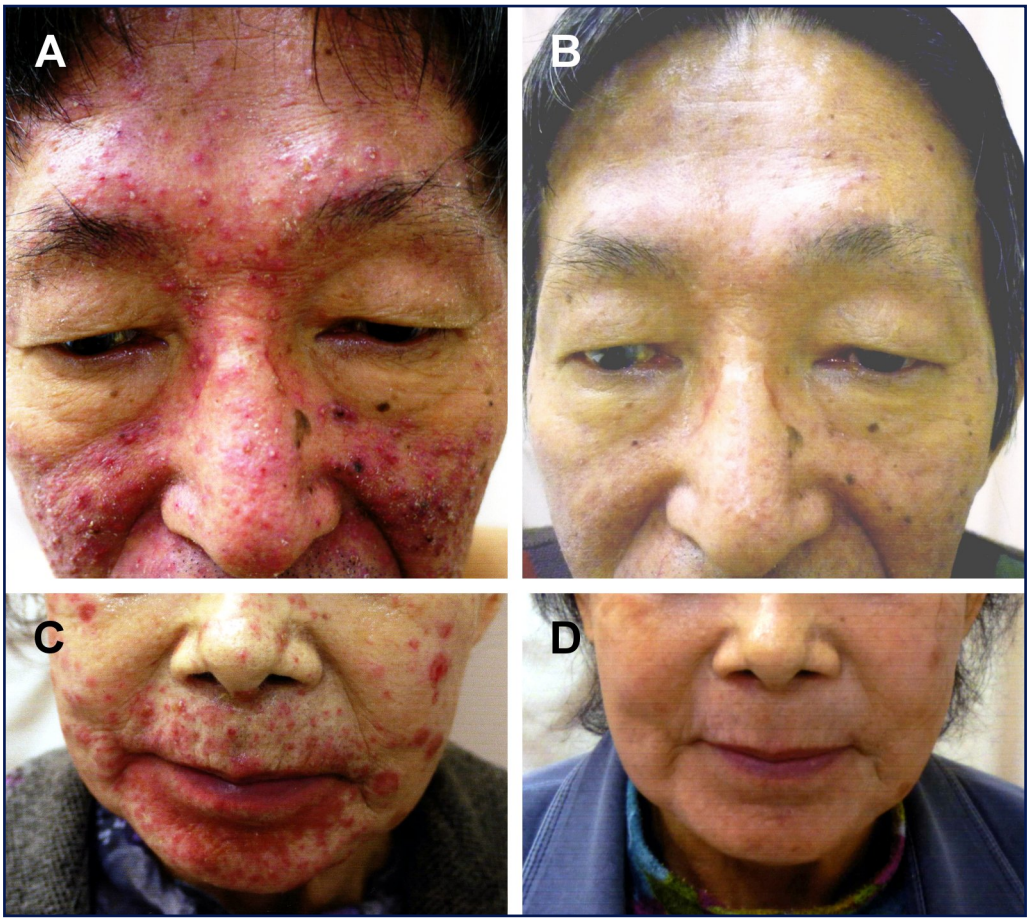

Figure 1

Clinical presentation of acneiform lesions before and after therapy.

A) Patient 4 diagnosed at first visit as grade II of CTCAE acneiform eruption and treated with oral tetracycline and ketoconazole ointment.

B) 14 days after treatment. CTCAE grade was down to I.

C) Patient 7 was given oral antihistamine treatement and ketoconazole ointment.

D) 21 days after treatment. Her CTCAE grade was down to grade I.

Table 1. Patients' characteristics.

	Age	Sex	Diagnosis	Itching VAS at first visit	Itching VAS after treatment
Patient 1	61	M	rectum ca. LNs meta.	30	10
Patient 2	54	F	sigmoid ca. Liver and lung meta.	40	10
Patient 3	64	M	colon ca. Liver meta.	30	10
Patient 4	67	M	colon ca. Liver meta.	40	15
Patient 5	68	F	sigmoido ca. Liver meta.	20	10
Patient 6	70	M	colon ca. Liver meta.	10	20
Patient 7	72	F	recutum ca. LNs meta.	35	10
average	65.1			29.2	12.1
				p<0.01	

ca. = carcinoma, meta. = metastasis, LNs = lymph nodes

Table 2. The period of Grade II. Statistical analysis by each treatment.

	use (days)	not use (days)	results of approval
tetracycline	14	47	**P < 0.05**
antihistamines	32	32	P > 0.05
COX2 inhibitor	70	17	**P < 0.05**
macrolide	42	31	P > 0.05
ketoconazole	16	54	**P < 0.05**
corticosteroid	34	21	P > 0.05
tacrolimus	21	34	P > 0.05
tetracycline+ketoconazole	14	46	**P < 0.05**

References

1. Bianchini D, Jayanth A, Chua YJ, Cunningham D. Epidermal growth factor receptor inhibitor-related skin toxicity: Mechanisms, treatment, and its potential role as predictive marker. *Clin Colorectal Cancer*. 2008; 7: 33-43. PMID: 18279575.
2. Lacouture ME, Melosky BL. Cutaneous reactions to anticancer agents targeting the epidermal growth factor receptor: A dermatology-oncology perspective. *Skin Therapy Lett*. 2007; 12: 1-5. PMID: 17762902.
3. Murillas R, Larcher F, Conti CJ, Santos M, Ullrich A, Jorcano JL. Expression of a dominant negative mutant of epidermal growth factor receptor in the epidermis of transgenic mice elicits striking alterations in hair follicle development and skin structure. *EMBO J*. 1995; 14: 5216-5223. PMID: 7489711.
4. Vezzoli P, Marzano AV, Onida F, Alessi E, Galassi B, Tomirotti M, Berti E. Cetuximab-induced acneiform eruption and the response to isotretinoin. *Acta Derm Venereol*. 2008; 88: 84-86. PMID: 18176767.
5. Alexandrescu DT, Vaillant JG, Dasanu CA. Effect of treatment with a colloidal oatmeal lotion on the acneform eruption induced by epidermal growth factor receptor and multiple tyrosine-kinase inhibitor. *Clin Exp Dermatol*. 2007; 32: 71-74. PMID: 17034418.
6. Jatoi A, Rowland K, Sloan JA, Gross HM, Fishkin PA, Kahanic SP, Novotny PJ, Schaefer PL, Johnson DB, Tschetter LK, Loprinzi CL. Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the North Central Cancer Treatment Group (N03CB). *Cancer*. 2008; 113: 847-853. PMID: 18543329.
7. Ashida M, Bito T, Budiyanto A, Ichihashi M, Ueda M. Involvement of EGF receptor activation in the induction of cyclooxygenase-2 in HaCaT keratinocytes after UVB. *Exp Dermatol*. 2003; 12: 445-452. PMID: 12930301.
8. Buchanan FG, Holla V, Katkuri S, Matta P, DuBois RN. Targeting cyclooxygenase-2 and the epidermal growth factor receptor for the prevention and treatment of intestinal cancer. *Cancer Res*. 2007; 67: 9380-9388. PMID: 17909047.
9. Peréz-Soler R, Saltz L. Cutaneous adverse effect with HER1/EGFR-targeted agents: is there a silver lining? *J Clin Oncol*. 2005; 23: 5235-5246. PMID: 16051966.