Prophylactic Effect of Oral Minocycline in Combination with Topical Steroid and Skin Care Against Panitumumab-induced Acneiform Rash in Metastatic Colorectal Cancer Patients

MAYA YAMADA[1], HIROTOSHI IIHARA[1], HIRONORI FUJII[1], MASASHI ISHIHARA[1], NOBUHISA MATSUHASHI[2], TAKAO TAKAHASHI[2], KAZUHIRO YOSHIDA[2] and YOSHINORI ITOH[1]

[1]*Department of Pharmacy, Gifu University Hospital, Gifu, Japan;*
[2]*Department of Surgical Oncology, Gifu University Graduate School of Medicine, Gifu, Japan*

Abstract. *Background: Although the anti-EGFR monoclonal antibody panitumumab is effective in treating colorectal cancer, the occurrence of severe skin disorders often discontinues therapy. Herein, we investigated by a retrospective chart review the effect of prophylactic oral minocycline in combination with skin treatment using moisturizer on the incidence of skin disorders and tumor response in metastatic colorectal cancer patients who received panitumumab. Patients and Methods: In a total of 55 patients, 38 patients were eligible, consisting the pre-emptive group (N=25) and reactive group (N=13). Acneiform rash and other adverse events were graded according to the CTCAE v4.0. Results: The occurrence of acneiform rash (grade ≥2) was significantly lower in pre-emptive group than in reactive group (44.0% vs. 84.6%, p=0.04). No significant differences in the occurrence of other adverse events were observed between the two groups. Tumor response was not significantly different between the two groups (36.0% vs. 7.7%, OR, 6.75; 95% confidence interval (CI)=0.75-60.76, p=0.12). Mean time to treatment failure was 149.7 days and 110.2 days in the pre-emptive group and reactive treatment group, respectively (HR=0.58; 95% CI= 0.26-1.28, p=0.18). Conclusion: Prophylactic oral minocycline combined with skin care reduced panitumumab-induced acneiform rash without a significant influence on tumor response.*

Panitumumab (Vectibix®, Takeda Pharmaceutical Co. Ltd.) is a fully human IgG2 monoclonal antibody targeting human epidermal growth factor receptor (EGFR), that obtained FDA approval in September 2006 for treating EGFR-expressing metastatic colorectal cancer during or after chemotherapy such as fluoropyrimidine compounds, oxaliplatin, and irinotecan.

However, the use of anti-EGFR antibody is associated with characteristic adverse drug reactions, including severe skin disorder, infusion reaction, and diarrhea (1-3). Among them, acneiform rash occurs most frequently from the early period of anti-EGFR therapy (4). In severe cases (grade ≥3), discontinuation of therapy or dose reduction is required (5-7). Although the precise mechanisms underlying the acneiform rash associated with anti-EGFR antibody is unclear, blockade of EGFR in cutaneous tissues may be involved in the pathogenesis of the symptom since EGFR is distributed throughout cutaneous tissues and involved in the proliferation and differentiation of epidermal cells. In this respect, the incidence or severity of skin rash is closely related to the therapeutic efficacy of anti-EGFR antibody. Lenz *et al*. (8) reported in 346 colorectal cancer patients treated with cetuximab that the incidence and severity of skin rash correlates well with the clinical response rate as well as the duration of survival (median overall survival: 1.7 months, 4.9 months and 9.4 months for grade 0, 1 and 2 rash, respectively). Similar data suggesting the positive correlation between cetuximab-induced rash and tumor response rate or survival were also reported by other investigators (9-11).

Several drugs have been tested for prevention of severe skin disorders associated with anti-EGFR therapy. Lacouture *et al*. (12) in a phase II randomized trial evaluating the effect of prophylactic skin treatment on skin toxicities of panitumumab in 95 colorectal cancer patients (STEPP study) reported that oral administration of doxycycline (100 mg twice a day), a tetracycline antibiotic agent, in combination with skin care using skin moisturizer, sunscreen, and topical steroid (1% hydrocortisone cream) for 6 weeks, inhibits the incidence of grade ≥2 skin toxicities, including pruritus, acneiform rash, and skin desquamation (29% *vs*. 62%, odds

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Correspondence to: M Yamada, Department of Pharmacy, Gifu University Hospital, 1-1 Yanagido, Gifu 501-1194, Japan. Tel: +81 582306000, Fax: +81 582307093, e-mail: maya@gifu-u.ac.jp

Key Words: acneiform rash, minocycline, skin care, panitumumab, colorectal cancer, tumor response, time to treatment failure.

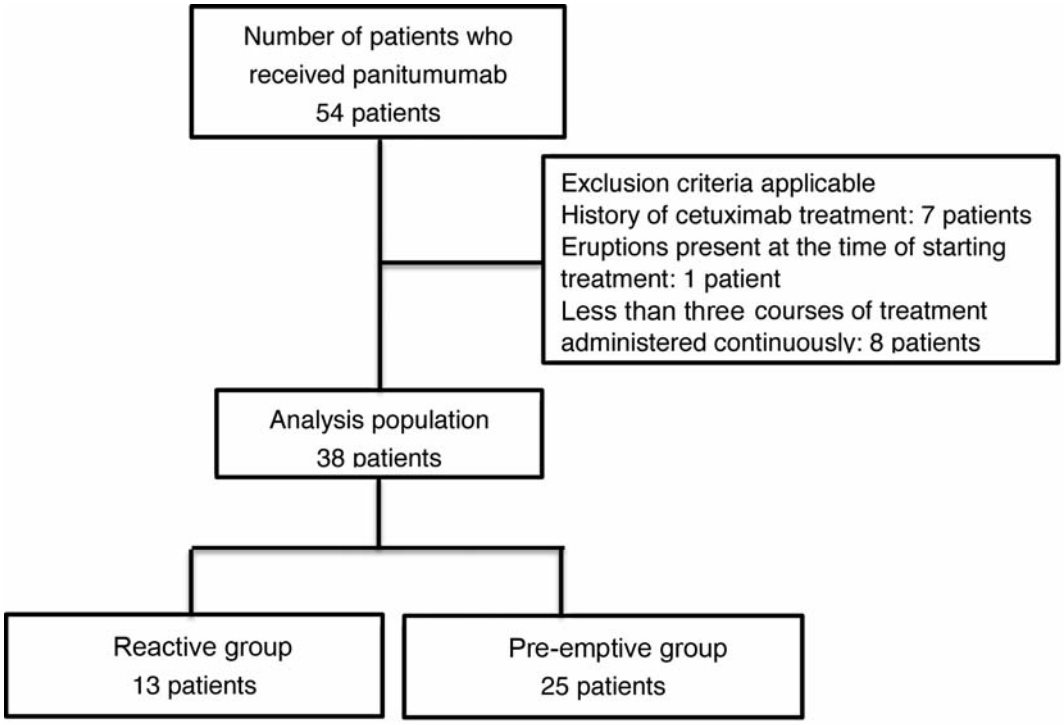

Figure 1. *Flow chart showing the inclusion and stratification of study individuals.*

ratio (OR)=0.3, 95% CI=0.1-0.6). On the other hand, Scope *et al.* (13) reported that oral treatment with another tetracycline antibiotic agent minocycline (100 mg/day) in combination with a topical retinoid analog tazarotene (0.05% cream) for 8 weeks significantly inhibits grade ≥2 itch but not rash associated with cetuximab.

In the present study, we evaluated the effect of minocycline (100 mg/day) in combination with skin care using skin moisturizer on the incidence of acneiform rash and other adverse events in colorectal cancer patients who received panitumumab.

Patients and Methods

Patients. The study cohort comprised of metastatic colorectal cancer patients who underwent cancer chemotherapy containing panitumumab at the Gifu University Hospital between July 2010 and May 2015. The exclusion criteria was as follows: patients previously treated with cetuximab, those observed to have rash before starting treatment, and those who received less than three courses of panitumumab.

The present study was conducted according to the guidelines for human studies determined by the ethical committee of the Gifu University Graduate School of Medicine and the Government of Japan, and was approved by the Medical Review Board of Gifu University Graduate School of Medicine (approval number, 26-153).

Treatment for prevention or therapy of acneiform rash. Patients received oral minocycline (100 mg once a day) combined with the standard skin care using skin moisturizer for prevention and reactive topical steroid (pre-emptive group) or remedy (reactive group) of skin disorders.

The reactive topical steroid could be administered any time when investigator deemed necessary for the management of emergent skin toxicity.

Evaluation of acneiform rash and other adverse reactions associated with panitumumab. Data were obtained from an electronic medical record and analyzed by a retrospective chart review. The symptoms of acneiform rash and other adverse events such as hypomagnesemia, oral mucositis, diarrhea, dry skin, pruritus, and paronychia were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. The incidence rates of acneiform rash and other adverse events were compared between the pre-emptive group and reactive group.

Relative dose intensity (RDI). RDI was calculated as the ratio of actual total amount of panitumumab injected/actual treatment duration divided by planned total amount/planned treatment duration.

Evaluation of tumor response. Tumor response was evaluated, according to the response evaluation criteria in solid tumors (RECIST) guideline version 1.1 (14). Response rate (complete and partial responses) and disease control rate (complete, partial

Table I. *Patient's characteristics*.

	Reactive group	Pre-emptive group	*p*-Value
Number of cases	13	25	
Gender (male/female)	9/4	16/9	0.97[a]
Age (minimum–maximum)	62.4(41-85)	62.5(35-87)	0.95[b]
Body height (cm)	163.1±9.1	162.3±9.8	0.81[c]
Body weight (kg)	61.0±14.7	59.7±12.0	0.76[c]
Body surface area	1.6±0.2	1.6±0.2	0.82[c]
Laboratory data			
Aspartate aminotransferase (U/L)	22.1±6.4	25.2±16.9	0.53[c]
Alanine aminotransferase (U/L)	16.8±7.6	19.1±9.3	0.46[c]
Serum creatinine (mg/dL)	0.9±0.6	0.7±0.2	0.14[c]
Blood urea nitrogen (mg/dL)	17.0±11.6	13.2±3.5	0.13[c]
Total bilirubin (mg/dL)	0.8±0.4	0.7±0.3	0.23[c]
White blood cells (/mm^3)	6364±2966	6130±2076	0.78[c]
Hemoglobin(g/dL)	12.0±2.2	12.4±2.1	0.55[c]
Platelet (×10^6/mm^3)	20.0±8.0	26.4±13.5	0.13[c]
Treatment regimens			
Panitumumab alone	8	4	0.04[b]
Panitumumab + mFOLFOX6	3	16	
Panitumumab + FOLFIRI	1	4	
Panitumumab + CPT-11	1	1	

Values represent mean±SD unless otherwise stated. [a]Chi-squared test, [b]Mann–Whitney *U*-test, [c]*t*-test.

responses and stable disease) were compared between the pre-emptive group and reactive group.

Statistical analyses. Data were analyzed using IBM SPSS version 22 (IBM Japan Ltd., Tokyo, Japan) and GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA). Patient characteristics were statistically compared between the pre-emptive group and reactive group. Non-parametric data were analyzed by the Mann-Whitney *U*-test or the Fisher's exact probability test, while parametric data were statistically compared between the two groups by *t*-test. The Kaplan-Meier estimate was used to analyze the development of acneiform rash and the duration of treatment courses and the Mantel–Cox log rank test was used for comparison of the median values of the period of acneiform rash onset or median courses of treatment in the two groups. $p<0.05$ was considered statistically significant.

Results

Patients' demographics. Among 54 patients shown in Figure 1, 16 patients were excluded based on the exclusion criteria and 38 patients were eligible, in which there were 25 patients in pre-emptive group and 13 patients in reactive group. As shown in Table I, no significant differences in patients' background were observed between the two groups, except for the treatment regimens.

Incidence of acneiform rash. As shown in Table II, the incidence of grade ≥2 acneiform rash was significantly lower in the pre-emptive group than in reactive group [44.0% *versus* 84.6%, OR, 0.143; 95% CI=0.026-0.783, $p=0.04$]. As a consequence, the incidence of grade 1 symptom was significantly higher in pre-emptive group as compared with reactive group (48.2% *versus* 7.8%, $p=0.02$).

Development of acneiform rash. The time course of the onset of grade ≥2 acneiform rash is shown in Figure 2. Median course of onset of grade ≥2 symptom was 3rd course for reactive group, while data were not determined for pre-emptive group (HR=0.33; 95% CI=0.12-0.90, $p=0.029$ by the Mantel-Cox log rank test).

Incidence of other adverse reactions to panitumumab. There were no significant differences in the incidence of other adverse reactions, including hypomagnesemia, oral mucositis, diarrhea, dry skin, cutaneous pruritic lesion, and paronychia, between pre-emptive group and reactive treatment group (Table III).

Tumor response rate. As shown in Table IV, tumor response rate (complete response plus partial response) tended to be higher in the pre-emptive group than in the reactive group (36.0% *vs*. 7.7%, OR=6.75; 95% CI=0.75-60.76, $p=0.12$). The disease control rate (sum of complete response, partial response and stable disease) was similar between the two groups (72.0% *vs*. 61.5%, $p=0.71$).

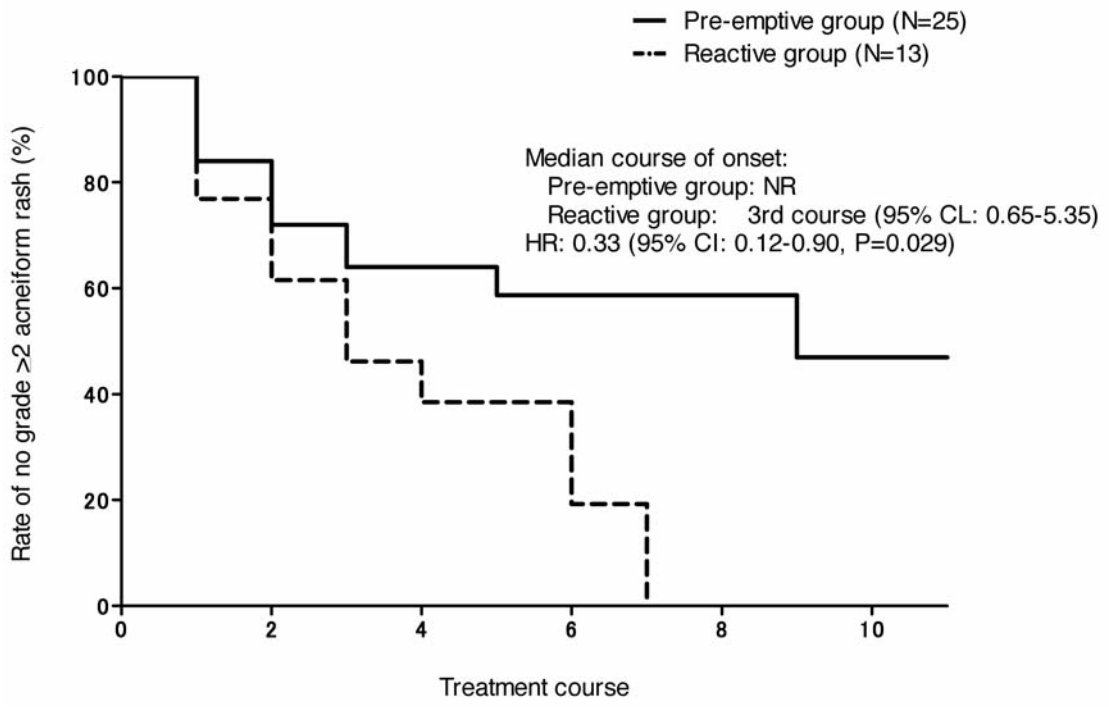

Figure 2. *Comparison of time to development of grade ≥2 acneiform rash between pre-emptive group and reactive group. Data were statistically compared by the Mantel-Cox log rank test.*

Table II. *Occurrence of acneiform rash.*

	Reactive group	Pre-emptive group	*p*-Value
Grade 0	1 (7.7%)	2 (8.0%)	1.00
Grade 1	1 (7.8%)	12 (48.2%)	0.02
Grade 2	9 (69.2%)	8 (32.0%)	0.06
Grade 3	2 (15.4%)	3 (12.0%)	1.00
Grade≥2	11 (84.6%)	11 (44.0%)	0.04
OR (95% confidence interval)	0.143 (0.026-0.783)		

Comparisons were made by the Chi-squared test.

Relative dose intensity (RDI). There was no significant difference in the RDI of panitumumab between the pre-emptive group and the reactive group (86.9% *versus* 83.5%, p=0.48).

Time to treatment failure. As shown in Figure 3, mean time to treatment failure tended to be longer in pre-emptive group than in reactive group (149.7 days *versus* 110.2 days, HR, 0.58; 95% CI=0.26-1.28, p=0.18), although median time to treatment failure was not different between the two groups (97.0 days *versus* 98.0 days).

Discussion

Acneiform rash is the most frequent adverse event during therapy using anti-EGFR monoclonal antibody. Mittmann and Seung (15) reported by a meta-analysis of data on the incidence of skin rash associated with anti-EGFR monoclonal antibody, that the rates of all grades and grades 3-4 symptoms are 74% (95% CI=68-81 from 7 studies) and 12% (95% CI=9-14 from 13 studies), respectively. In generally consistent with their data, in the present study, acneiform rash of all grades and grade 3 occurred in 92%

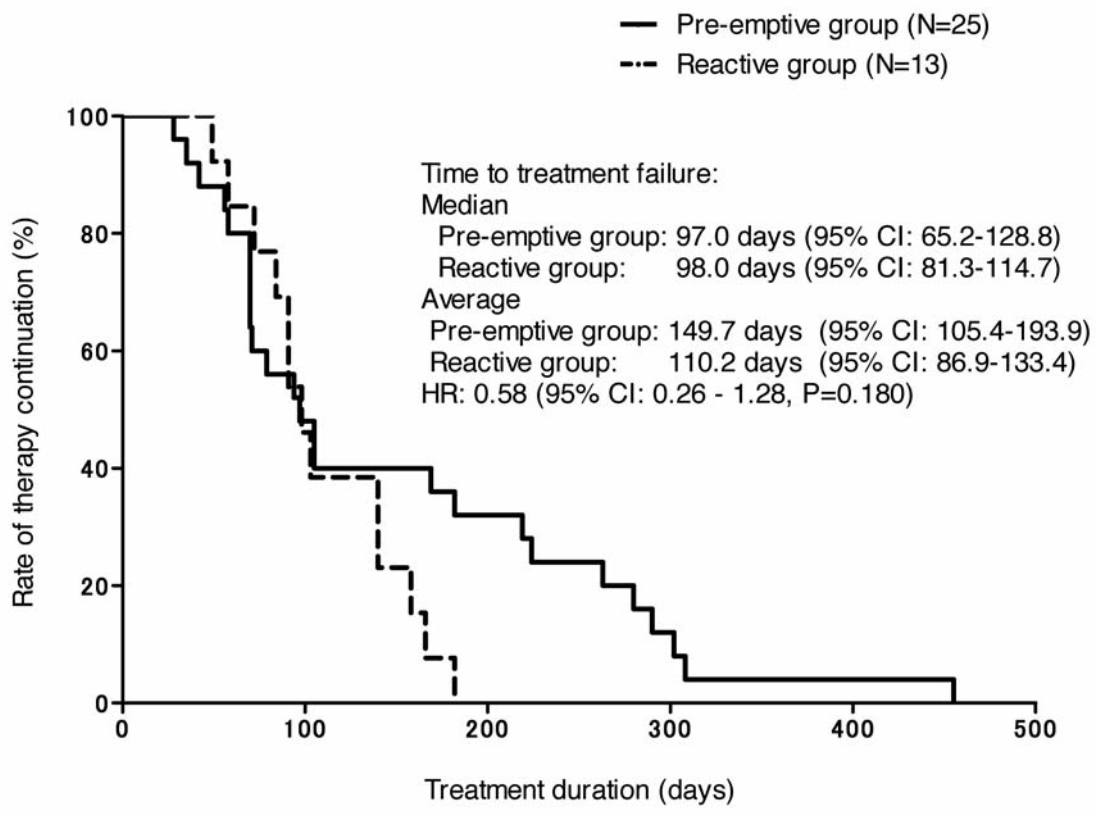

Figure 3. *Comparison of time to treatment failure between pre-emptive group and reactive group. Data were statistically compared by the Mantel-Cox log rank test.*

and 15% of patients who received panitumumab, respectively, in the reactive group.

On the other hand, it has been considered that the incidence of skin toxicities is closely related to the therapeutic effect of anti-EGFR therapy. Lenz *et al*. (8) reported a significant relationship between the severity of skin rash and overall survival in patients receiving cetuximab. Similar data were also reported by other investigators, suggesting that the occurrence of moderate-to-severe cetuximab-induced rash is associated with improved tumor response rate or survival (9-11). Therefore, it is likely that prophylaxis of moderate-to-severe skin toxicities is particularly important to maximize the survival advantage of anti-EGFR therapy.

Tetracyclines such as doxycycline and minocycline possess anti-inflammatory action in addition to the antibiotic action, and thus, used for the treatment of various skin disorders, including inflammatory acne, and neutrophilic dermatoses (16). Inhibition of lymphocyte activation and neutrophil chemotaxis is considered to be implicated in the anti-inflammatory action of tetracyclines (17). Moreover, Ishikawa *et al*. (18) reported that both minocycline and doxycycline inhibit the production of interleukin-8 (IL-8), a pro-inflammatory cytokine, induced by the activation of protease-activated receptor 2 (PAR2) in normal human epidermal keratinocytes. They also showed that tetracyclines reduce the potentiation by TNF-α or interleukin-1β of PAR2-mediated IL-8 production, in which minocycline is more potent than doxycycline. This may be related to the fact that minocycline is superior to doxycycline in lipid solubility (19). A phase II randomized trial evaluating the effect of prophylactic skin treatment on skin toxicities of panitumumab (STEPP study) indicated that pre-emptive doxycycline treatment group reveals an improvement of skin toxicities, including pruritus, acneifom rash, skin desquamation without affecting the tumor response rate or progression-free survival (12). On the other hand, Scope *et al*. (13) have shown that pre-emptive minocycline plus tazarotene group shows a significant reversal of pruritus (20% *vs*. 50%, $p<0.05$) without significant improvement of acneiform rash (20% *vs*. 42%, $p=0.13$) in patients receiving cetuximab. Very recently, a randomized controlled trial comparing the pre-emptive or reactive treatment with minocycline in combination with skin care using moisturizer, sunscreen and topical corticosteroid on the skin

Table III. *Appearance of other adverse reactions to panitumumab.*

	Reactive group		Pre-emptive group		*p*-Value
	Number of cases	Incidence (%)	Number of cases	Incidence (%)	
Hypomagnesemia					
Grade 0	8	61.5	15	60.0	
Grade 1	3	23.1	6	24.0	
Grade 2	2	15.4	4	16.0	
Grade≥2	2	15.4	4	16.0	1.00
Oral mucositis					
Grade 0	8	61.5	7	28.0	
Grade 1	2	15.4	9	36.0	
Grade 2	3	23.1	7	28.0	
Grade 3	0	0.0	2	8.0	
Grade≥2	3	23.1	9	36.0	0.49
Diarrhea					
Grade 0	9	69.2	13	52.0	
Grade 1	2	15.4	7	28.0	
Grade 2	1	7.7	4	16.0	
Grade 3	1	7.7	1	4.0	
Grade≥2	2	15.4	5	20.0	1.00
Dry skin					
Grade 0	2	15.4	3	12.0	
Grade 1	7	53.8	7	28.0	
Grade 2	4	30.8	15	60.0	
Grade≥2	4	30.8	15	60.0	0.17
Pruritus					
Grade 0	8	61.5	9	36.0	
Grade 1	3	23.1	9	36.0	
Grade 2	2	15.4	7	28.0	
Grade≥2	2	15.4	7	28.0	0.46
Paronychia					
Grade 0	7	53.8	11	44.0	
Grade 1	3	23.1	4	16.0	
Grade 2	3	23.1	8	32.0	
Grade 3	0	0.0	2	8.0	
Grade≥2	3	23.1	10	40.0	0.47

Comparisons were made by the Chi-square test.

toxicities of panitumumab in 95 colorectal cancer patients (J-STEPP study) has been reported (20). The showed that the incidence of grade >2 skin toxicities is significantly lower in pre-emptive group than in reactive group (21% *vs.* 63%, $p<0.001$). However, in their report, survival is likely to be slightly and not significantly shorter in pre-emptive treatment group: median OS: 8.2 months *versus* 12.1 months (HR=1.19; 95% CI=0.75-1.90, $p=0.469$), median PFS was 3.6 months *versus* 4.0 months (HR=1.20; 95% CI=0.78-1.84, $p=0.413$), median time to treatment failure was 3.0 months *versus* 3.5 months (HR=1.23; 95% CI=0.80–1.89, $p=0.343$).

Generally consistent with previous findings, in the present study, prophylactic oral treatment with minocycline in combination with skin treatment using skin moisturizer was effective in suppressing the development of panitumumab-induced acneiform rash.

However, the effect of minocycline on the tumor response or survival were not similar between our data and those in the J-STEPP study (20). In the present study, mean time to treatment failure tended to be longer in pre-emptive group than in reactive group (149.7 days *vs.* 110.2 days, HR=0.58; 95% CI=0.26-1.28, $p=0.18$). Moreover, in the present study, tumor response rate tended to be higher in the pre-emptive group (36.0% *vs.* 7.6%, $p=0.12$), which was similar to the data in the STEPP study (12).

It has been shown that systemic administration of minocycline enhances cyclophosphamide-induced tumor-killing effect and inhibition of lung metastasis in C57BL mice implanted subcutaneously with Lewis lung tumor cells (21). Therefore, a slight and not significant increase in tumor response rate by minocycline observed in the present study may be due to its potentiating action on anticancer drugs.

A large scale prospective study is required to clarify the effect of prophylactic minocycline on the therapeutic effects such as tumor response and survival.

Table IV. *Comparison of tumor response between the reactive group and the pre-emptive group.*

Tumor response	Reactive group (N=13)		Pre-emptive group (N=25)		*p*-Value
	N	Incidence (%)	N	Incidence (%)	
Complete response	1	7.7	0	0	
Partial response	0	0	9	36.0	
Stable disease	7	53.8	9	36.0	
Progressive disease	5	38.5	5	20.0	
Not assessable	0	0	2	8.0	
Response rate	1	7.7	9	36.0	0.12
Disease control rate	8	61.5	18	72.0	0.71

Comparisons were made by the Chi-square test.

In conclusion, prophylactic oral minocycline together with skin treatment using moisturizer was found to be effective in suppressing the development of grade ≥2 acneiform rash induced by panitumumab without any significant influence on the tumor response or time to treatment failure in colorectal cancer patients.

Conflicts of Interest

The Authors declare that no conflict of interest, with any company and other organization, exists pertaining to this article mentioned regarding the content, conclusion and significance of the research, as well as the opinions therein.

References

1 Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, Juan T, Sikorski R, Suggs S, Radinsky R, Patterson SD and Chang DD: Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol *26*: 1626-1634, 2008.

2 Muro K, Yoshino T, Doi T, Shirao K, Takiuchi H, Hamamoto Y, Watanabe H, Yang BB and Asahi D: A phase 2 clinical trial of panitumumab monotherapy in Japanese patients with metastatic colorectal cancer. Jpn J Clin Oncol *39*: 321-326, 2009.

3 Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, Canon JL, Van Laethem JL, Maurel J, Richardson G, Wolf M and Amado RG: Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol *25*: 1658-1664, 2007.

4 Hynes NE and Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. Nat Rev Cancer *5*: 341-354, 2005.

5 Boone SL, Rademaker A, Liu D, Pfeiffer C, Mauro DJ and Lacouture ME: Impact and management of skin toxicity associated with anti-epidermal growth factor receptor therapy: survey results. Oncology *72*: 152-159, 2007.

6 Eilers RE Jr, Gandhi M, Patel JD, Mulcahy MF, Agulnik M, Hensing T and Lacouture ME: Dermatologic infections in cancer patients treated with epidermal growth factor receptor inhibitor therapy. J Natl Cancer Inst *102*: 47-53, 2010.

7 Wagner LI and Lacouture ME: Dermatologic toxicities associated with EGFR inhibitors: the clinical psychologist's perspective. Impact on health-related quality of life and implications for clinical management of psychological sequelae. Oncology (Williston Park) *21(11 Suppl 5)*: 34-36, 2007.

8 Lenz HJ, Van Cutsem E, Khambata-Ford S, Mayer RJ, Gold P, Stella P, Mirtsching B, Cohn AL, Pippas AW, Azarnia N, Tsuchihashi Z, Mauro DJ and Rowinsky EK: Multicenter phase II and translational study of cetuximab in metastatic colorectal carcinoma refractory to irinotecan, oxaliplatin, and fluoropyrimidines. J Clin Oncol *24*: 4914-4921, 2006.

9 Vincenzi B, Santini D, Rabitti C, Coppola R, Beomonte Zobel B, Trodella L and Tonini G: Cetuximab and irinotecan as third-line therapy in advanced colorectal cancer patients: a single centre phase II trial. Br J Cancer *94*: 792-797, 2006.

10 Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, Berry SR, Krahn M, Price T, Simes RJ, Tebbutt NC, van Hazel G, Wierzbicki R, Langer C and Moore MJ: Cetuximab for the treatment of colorectal cancer. N Engl J Med *357*: 2040-2048, 2007.

11 Orditura M, De Vita F, Galizia G, Lieto E, Vecchione L, Vitiello F, Martinelli E and Ciardiello F: Correlation between efficacy and skin rash occurrence following treatment with the epidermal growth factor receptor inhibitor cetuximab: a single institution retrospective analysis. Oncol Rep *21*: 1023-1028, 2009.

12 Lacouture ME, Mitchell EP, Piperdi B, Pillai MV, Shearer H, Iannotti N, Xu F and Yassine M: Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-Emptive Skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol *28*: 1351-1357, 2010.

13 Scope A, Agero AL, Dusza SW, Myskowski PL, Lieb JA, Saltz L, Kemeny NE and Halpern AC: Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. J Clin Oncol *25*: 5390-5396, 2007.

14 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45*: 228-247, 2009.

15 Mittmann N and Seung SJ: Rash rates with EGFR inhibitors: meta-analysis. Curr Oncol *18*: e54-63, 2011.

16 Sapadin AN and Fleischmajer R: Tetracyclines: nonantibiotic properties and their clinical implications. J Am Acad Dermatol *54*: 258-265, 2006.

17 Thong YH and Ferrante A: Inhibition of mitogen-induced human lymphocyte proliferative responses by tetracycline analogues. Clin Exp Immunol *35*: 443-446, 1979.

18 Ishikawa C, Tsuda T, Konishi H, Nakagawa N and Yamanishi K: Tetracyclines modulate proteinase-activated reseptor 2-mediated proinflammatory reactions in epidermal keratinocytes. Antimicrob Agents Chemother *53*: 1760-1765, 2009.

19 Barza M, Brown RB, Shanks C, Gamble C and Weinstein L: Relation between lipophilicity and pharmacological behavior of minocycline, doxycycline, tetracycline, and oxytetracycline in dogs. Antimicrob Agents Chemother *8*: 713-720, 1975.

20 Kobayashi Y, Komatsu Y, Yuki S, Fukushima H, Sasaki T, Iwanaga I, Uebayashi M, Okuda H, Kusumi T, Miyagishima T, Sogabe S, Tateyama M, Hatanaka K, Tsuji Y, Nakamura M, Konno J, Yamamoto F, Onodera M, Iwai K, Sakata Y, Abe R, Oba K and Sakamoto N: Randomized controlled trial on the skin toxicity of panitumumab in Japanese patients with metastatic colorectal cancer: HGCSG1001 study; J-STEPP. Future Oncol *11*: 617-627, 2015.

21 Sotomayor EA, Teicher BA, Schwartz GN, Holden SA, Menon K, Herman TS and Frei E 3rd: Minocycline in combination with chemotherapy or radiation therapy *in vitro* and *in vivo*. Cancer Chemother Pharmacol *30*: 377-384, 1992.

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