RESEARCH ARTICLE

For reprint orders, please contact: reprints@futuremedicine.com

Randomized controlled trial on the skin toxicity of panitumumab in Japanese patients with metastatic colorectal cancer: HGCSG1001 study; J-STEPP

Yoshimitsu Kobayashi¹, Yoshito Komatsu^{*2}, Satoshi Yuki¹, Hiraku Fukushima², Takahide Sasaki¹, Ichiro Iwanaga³, Minoru Uebayashi³, Hiroyuki Okuda⁴, Takaya Kusumi⁵, Takuto Miyagishima⁶, Susumu Sogabe⁷, Miki Tateyama⁸, Kazuteru Hatanaka⁹, Yasushi Tsuji¹⁰, Michio Nakamura¹¹, Jun Konno¹², Fumiyasu Yamamoto¹³, Manabu Onodera¹⁴, Kazuhiro Iwai¹⁵, Yuh Sakata¹⁶, Riichiro Abe¹⁷, Koji Oba¹⁸ & Naoya Sakamoto¹

ABSTRACT **Aim:** We planned a randomized, open-label trial to evaluate differences between pre-emptive and reactive skin treatment for panitumumab (Pmab)-associated skin toxicities in Japanese patients with metastatic colorectal cancer. **Patients & methods:** Patients receiving third-line Pmab-containing regimens were randomized to pre-emptive or reactive treatment. The primary end point was the cumulative incidence of $\geq$ grade 2 skin toxicities during 6 weeks. Retrospectively, a dermatologist reviewed skin toxicities, in a blinded manner. **Results:** A total of 95 patients were enrolled (pre-emptive: 47, reactive: 48). The primary end point was achieved (21.3 and 62.5% [risk ratio: 0.34; $p < 0.001$], for pre-emptive and reactive treatment, respectively). A similar trend was observed in central review. **Conclusion:** Pre-emptive skin treatment could reduce the severity of Pmab-associated skin toxicities in Japanese metastatic colorectal cancer patients.

The EGF receptor (EGFR) has been validated as a therapeutic target in metastatic colorectal cancer (mCRC). Panitumumab (Pmab) [1,2], a fully human immunoglobulin G2 monoclonal antibody, has demonstrated efficacy and safety for *KRAS* wild-type mCRC in pivotal global Phase III studies [3–6], and is used widely around the world. Some clinical trials have also revealed that the characteristic

KEYWORDS

- colorectal cancer
- Japanese • panitumumab
- pre-emptive • skin toxicities

¹Department of Gastroenterology & Hepatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

²Department of Cancer Center, Hokkaido University Hospital, Sapporo, Hokkaido, Japan

³Department of Gastroenterology, Japanese Red Cross Kitami Hospital, Kitami, Japan

⁴Department of Medical Oncology, Keiyukai Sapporo Hospital, Sapporo, Japan

⁵Department of Surgery, Keiyukai Sapporo Hospital, Sapporo, Japan

⁶Department of Internal Medicine, Kushiro Rosai Hospital, Kushiro, Japan

⁷Department of Medical Oncology, Kushiro Rosai Hospital, Kushiro, Japan

⁸Department of Internal Medicine, Tomakomai Nisshou Hospital, Tomakomai, Japan

⁹Department of Gastroenterology, Hakodate Municipal Hospital, Hakodate, Japan

¹⁰Department of Medical Oncology, Tonan Hospital, Sapporo, Japan

¹¹Department of Gastroenterology, Sapporo City General Hospital, Sapporo, Japan

¹²Department of Internal Medicine, Hakodate Central General Hospital, Hakodate, Japan

¹³Department of Gastroenterology, Tomakomai City Hospital, Tomakomai, Japan

¹⁴Department of Internal Medicine and Gastroenterology, Abashiri Kosei General Hospital, Abashiri, Japan

¹⁵Department of Surgery, Oji General Hospital, Tomakomai, Japan

¹⁶Misawa City Hospital, Misawa, Japan

¹⁷Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

¹⁸Translational Research & Clinical Trial Center, Hokkaido University Hospital, Sapporo, Japan

*Author for correspondence: Tel./Fax: +81 11 706 5657; ykomatsu@ac.cyberhome.ne.jp

adverse event of anti-EGFR treatment, various skin toxicities, can occur in more than 90% of patients [7–9], and may lead to decreased quality of life (QOL) [10] and discontinuation of chemotherapy.

However, response and survival have been shown to be correlated with the severity of skin toxicities in some studies [3,11–14], so it is important to manage skin toxicities in order to achieve the maximum efficacy of EGFR inhibitors [15–18]. Lacouture *et al.* reported that pre-emptive skin treatment might reduce the incidence of $\geq$ grade 2 skin toxicities compared with reactive treatment in the STEPP study [19]. Meanwhile, there are currently no data regarding the efficacy of pre-emptive skin treatment in Asian populations receiving Pmab.

We planned a randomized, open-label clinical trial to verify the differences between pre-emptive and reactive treatments for Pmab-associated skin toxicities in Japanese patients with mCRC.

Patients & methods

• Study design & participants

This was an open-label, multicenter randomized clinical trial (registered with UMIN, number UMIN000004883 [20]).

We recruited patients from 16 institutions belonging to the Hokkaido Gastrointestinal Cancer Study Group (HGCSG) in Japan. Inclusion criteria were pathologically confirmed *KRAS* wild-type mCRC with evaluable disease, and two prior chemotherapy regimens for mCRC (adjuvant chemotherapy with fluoropyrimidine alone was not included in the count of primary treatment if disease recurrence occurred during or within 6 months from completion).

Other key eligibility criteria were age ≥ 20 years, Eastern Cooperative Oncology Group performance status score ≤ 2 , and adequate organ function. Patients were excluded if they had received prior anti-EGFR therapy.

The trial was carried out in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committees at participating sites. All patients signed informed consent before any study-related procedures were performed.

• Randomization & masking

Patients were randomly assigned, in a one-to-one ratio, to either pre-emptive skin treatment or reactive skin treatment. Randomization was done centrally with a computer-generated

sequence and a permuted block technique to ensure balance between treatment groups and stratification factors (age, sex, institution and chemotherapy regimen). Investigators registered the patient on web-pages created for this study, and the patient was automatically assigned to one of two treatment groups. This was an open-label trial, so investigators and patients were not masked to treatment allocation.

• Procedures

The primary end point was the cumulative incidence of $\geq$ grade 2 skin toxicities during 6 weeks. Secondary end points were centrally reviewed skin toxicities by a dermatologist, time to first occurrence of skin toxicities according to grade, time to recover to $\leq$ grade 1 in case of $\geq$ grade 2 skin toxicities occurring, QOL, safety, progression-free survival (PFS; defined as the time between randomization and disease progression or death from any cause, whichever occurred earlier), overall survival (OS; defined as the time between randomization and death from any cause or the date of last follow-up), time-to-treatment-failure (TTF; defined as the time between randomization and disease progression or death from any cause, or discontinuation of any protocol treatment, whichever occurred earlier) and overall response rate (ORR). A stratified analysis by chemotherapy regimen was also performed.

The skin treatment regimen was administered from 1 day before the first Pmab-contained chemotherapy to 8 weeks. The pre-emptive treatment regimen consisted of skin moisturizer, sunscreen, topical steroid and minocycline. The reactive treatment regimen consisted of only skin moisturizer (and sunscreen if patients requested).

Skin moisturizer and topical steroid (0.5% hydrocortisone cream) were applied to face, hands, feet, neck, back and chest both in the morning on rising and evening (bedtime). Twice-daily application of moisturizer and topical steroid was chosen in order to avoid any potential patient confusion with once-daily application of each (as in STEPP), and also due to the evening bathing customs of Japanese patients. Sunscreen (SPF 25, PFA not more than eight but less than four and UVA and UVB protection) was applied to sun-exposed areas before going out. Minocycline 100 mg was taken once a day. All patients were given a diary which contained notes about being careful to prevent skin

toxicities in daily life and instructions on skin moisturizer, sunscreen and topical steroid (the latter for the pre-emptive treatment group only).

The diary, which also included check lists for adherence of skin treatment and symptoms, was shared with investigators at every clinic visit and used for supplemental case report form data entry.

Pmab was administered at 6.0 mg/kg every 2 weeks. If $\geq$ grade 3 skin toxicity occurred, administration of Pmab was suspended, and Pmab dose reduction was performed after recovery to $\leq$ grade 2. The chemotherapy regimen was chosen by each investigator.

Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Investigators evaluated skin toxicities at every visit, and checked the date of occurrence of the worst grade skin toxicities, first $\geq$ grade 2 skin toxicity, and recovery to $\leq$ grade 1.

All patients were monitored at least biweekly from the start of treatment to week 12 for assessment of skin toxicities, and adherence to the randomized skin treatment regimen.

If $\geq$ grade 2 skin toxicity occurred during the treatment period (8 weeks), investigators could take appropriate measures in both groups. From week 8 and thereafter, investigators had the option to continue patients on the assigned skin treatment regimen.

A central review for skin toxicities was also performed by one dermatologist. Investigators had to take photographs of patients' skin at every clinic visit. The dermatologist was blinded to the photographs, and evaluated skin toxicity by National Cancer Institute CTCAE version 3.0.

Patient-reported QOL was assessed using the Dermatology Life Quality Index (DLQI) at screening, 3 weeks, 7 weeks and 13 weeks. The DLQI consists of ten simple questions to assess QOL in patients with skin disorders, and is scored on a scale of 0–30; higher scores indicate greater QOL impairment [21].

Tumor response was assessed every 6 weeks by investigators using the same method as at baseline (CT), and was assessed according to Response Evaluation Criteria in Solid Tumors version 1.0 [22].

• Statistical analysis

Sample size calculation was based on the χ^2 test: 92 analyzable patients (46 for each group) were

required to detect a risk reduction from 62% of the cumulative incidence of $\geq$ grade 2 skin toxicities during 6 weeks in the reactive treatment group to 29% in the pre-emptive group (based on the results of the STEPP study) [19], with 90% power and two-sided 5% significance level. With the assumption of 10% drop-out, we set 102 patients as the targeted sample size.

All analyses were conducted based on the intention-to-treat principle. Patient characteristics were expressed as mean $\pm$ SD or proportions. Comparison of the primary and other binary end points between two groups was calculated by χ^2 test. When expected cell counts were less than five in the contingency table, the Fisher exact test was used. Risk ratio (RR) was also reported with its 95% CI. Time to event end points were analyzed by the Kaplan–Meier method and compared by log-rank test. Hazard ratio (HR) was calculated using the Cox proportional hazard model. Comparison of the “time to recover to $\leq$ grade 1 in the case of $\geq$ grade 2 skin toxicities occurring” was analyzed, with adjustment for possible confounders, in the Cox proportional hazard model. A linear mixed effect model was used to compare the DLQI in the two groups across repeated cycles of treatment. The mixed effect model included fixed factors of treatment, time (at screening, and 3, 7 and 13 weeks), and treatment interaction, and a random effect of patients. Time was treated as a continuous variable to compare the linear change between two groups. All analyses were performed using SAS software v9.3 (SAS Institute Inc., NC, USA).

Results

Between 7 July 2010 and 31 March 2013 (data cutoff: 30 June 2013), 95 patients were randomly assigned to pre-emptive ($n = 47$) or reactive ($n = 48$) skin treatment. We closed patient accrual because ineligible patients were fewer than assumed, ensuring an adequate number of cases for analysis. One patient allocated to the pre-emptive treatment group had never been administered any study treatment. The intention-to-treat population consisted of all 95 patients.

Baseline characteristics were similar between the two groups (Table 1). At the data collection cut-off date, the 12-week observation period for skin toxicities was completed for all patients; median follow-up time was 24.9 months (interquartile range: 19.0–27.8) in the pre-emptive treatment group and 30.7 months (interquartile

Table 1. Characteristics of patients at baseline.

Characteristic	Reactive skin treatment group (n = 48)	Pre-emptive skin treatment group (n = 47)
Sex:		
– Male	32 (66.7)	25 (53.2)
– Female	16 (33.3)	22 (46.8)
Age (years)	68 (54–81)	70 (48–88)
ECOG performance status:		
– 0	30 (62.5)	32 (68.1)
– 1	13 (27.1)	13 (27.7)
– 2	5 (10.4)	2 (4.2)
Primary site:		
– Colon	30 (62.5)	34 (72.3)
– Rectum	18 (37.5)	13 (27.7)
Number of metastatic sites:		
– 1	18 (37.5)	9 (19.1)
– ≥2	30 (62.5)	38 (80.9)
EGFR status:		
– Positive	29 (60.4)	25 (53.2)
– Negative	12 (25.0)	9 (19.1)
– Not tested	7 (14.6)	13 (27.7)
Primary lesion:		
– Presence	11 (22.9)	10 (21.3)
– Absence	37 (77.1)	37 (78.7)
Regimen:		
– Pmab alone	29 (60.4)	32 (68.1)
– Irinotecan and Pmab	18 (37.5)	12 (25.5)
– FOLFIRI and Pmab	1 (2.1)	3 (6.4)

Data are n (%) or median (range).
ECOG: Eastern Cooperative Oncology Group; EGFR: EGF receptor; FOLFIRI: Irinotecan, fluorouracil and folinic acid; Pmab: Panitumumab.

range: 16.0–33.2) in the reactive treatment group.

The cumulative incidence of ≥grade 2 skin toxicities (according to each investigator’s assessment) in 6 weeks was 21.3% (10/47; 95% CI: 9.6–33.0%) in the pre-emptive group compared with 62.5% (30/48; 95% CI: 48.8–76.2%) in the reactive group (RR: 0.34; 95% CI: 0.19–0.62; $p < 0.001$; Table 2), the risk reduction was 65.9%. A similar trend was observed at 8 weeks (skin treatment period) and 12 weeks (skin toxicity observation period), with an incidence of 25.5 and 66.7% in the pre-emptive and reactive groups, respectively (8 weeks), and 42.6 and 75.0%, respectively (12 weeks).

According to investigators’ assessment, median time to first occurrence of ≥grade 2 skin toxicities was not reached in the pre-emptive group, and was 3.2 weeks (HR: 0.35; 95% CI: 0.20–0.61; log-rank $p < 0.001$) in the reactive group (Figure 1A).

The central review of skin toxicities, based on photographs, was performed by a dermatologist (blinded to patient clinical information).

In total, paired baseline and follow-up photographs were available for 87 (91.6%) out of 95 patients. In the review, the cumulative incidence of ≥grade 2 skin toxicities in 6 weeks was 18.6% in the pre-emptive group compared with 50.0% in the reactive group (RR: 0.37; 95% CI: 0.19–0.74; Table 2). The concordance rate for skin toxicities rated as 0–1 (<grade 2) or as 2–3 (≥grade 2) during the 6 weeks between investigators’ assessment and the central review was 75.9%; 79.1% (34/43) in the pre-emptive group, and 72.7% (32/44) in the reactive treatment group (Table 3). According to the central review, median time to first occurrence of ≥grade 2 skin toxicities was not reached in the pre-emptive group, and was 5.4 weeks (HR: 0.50; 95% CI: 0.27–0.92; log-rank $p = 0.020$) in the reactive group (Figure 1B).

Median OS was 8.2 months (95% CI: 5.8–13.1) in the pre-emptive group and 12.1 months (95% CI: 6.7–21.7) in the reactive group (HR: 1.19; 95% CI: 0.75–1.90; log-rank $p = 0.469$). Median PFS was 3.6 months (95% CI: 2.4–4.9) and 4.0 months (95% CI: 2.8–4.5), respectively (HR: 1.20; 95% CI: 0.78–1.84; log-rank $p = 0.413$). Median TTF was 3.0 months (95% CI: 2.3–4.6) and 3.5 months (95% CI: 2.1–4.6), respectively (HR: 1.23; 95% CI: 0.80–1.89; log-rank $p = 0.343$). Five patients in each group discontinued treatment (Pmab-containing chemotherapy). In the pre-emptive treatment group, three patients discontinued treatment because of adverse events (rash acneiform in two patients), and two patients discontinued because of patient requests (not induced by adverse events). In the reactive group, two patients discontinued treatment because of adverse events (rash acneiform in one patient), two patients discontinued because of investigator’s decision and one patient discontinued because of conversion surgery (liver metastasis resection).

Out of 95 randomized patients, 89 patients with measurable lesion(s) were included in the assessment of objective responses. There was no statistically significant difference in ORR between the two groups (13.3% in the pre-emptive treatment group and 18.2% in the reactive treatment group, $p = 0.530$).

The safety population included 94 patients who were treated with at least one cycle of their allocated study treatment. Adverse events are summarized in Table 4. Main adverse events (incidence of ≥grade 3 was more than 5% in

both groups) were rash acneiform, hypomagnesemia, and anemia. No adverse events were associated with the assigned skin treatment regimen. There were no treatment-related deaths.

The stratified analysis by chemotherapy regimen was also performed; Pmab alone (n = 61), irinotecan-based regimen (n = 34; irinotecan plus Pmab [n = 30] and FOLFIRI plus Pmab [n = 4]). In the Pmab alone group, the cumulative incidence of $\geq$ grade 2 skin toxicities in 6 weeks was 28.1% in the pre-emptive group compared with 69.0% in the reactive group

(RR: 0.41; 95% CI: 0.22–0.75; p = 0.001). A similar trend was observed in the irinotecan-based regimen group, 6.7 and 52.6% (RR: 0.13; 95% CI: 0.02–0.88; p = 0.008).

Overall completion of the DLQI, for comparisons between baseline and the end of observation period of skin toxicities (12 weeks), were performed. The questionnaire collection rate was 58.9% (27 out of 47 patients in the pre-emptive group, and 29 of 48 patients in the reactive group). Baseline characteristics of the 56 patients were well balanced between the

Table 2. Cumulative incidence of $\geq$ grade 2 skin toxicities by investigators' assessment and by central review.

Assessment	Reactive skin treatment	Pre-emptive skin treatment
Investigators' assessment		
n	48	47
6 weeks		
$\geq$ Grade 2 skin toxicities, n (%)	30 (62.5)	10 (21.3)
Risk ratio (95% CI)		0.34 (0.19–0.62)
p-value		<0.001
Grade 2, n (%)	23 (47.9)	9 (19.1)
95% CI	33.8–62.1	7.9–30.4
$\geq$ Grade 3, n (%)	7 (14.6)	1 (2.1)
95% CI	4.6–24.6	0–6.3
8 weeks		
$\geq$ Grade 2 skin toxicities, n (%)	32 (66.7)	12 (25.5)
Risk ratio (95% CI)		0.38 (0.23–0.65)
p-value		<0.001
12 weeks		
$\geq$ Grade 2 skin toxicities, n (%)	36 (75.0)	20 (42.6)
Risk ratio (95% CI)		0.57 (0.39–0.82)
p-value		0.001
Central review		
n	44	43
6 weeks		
$\geq$ Grade 2 skin toxicities, n (%)	22 (50.0)	8 (18.6)
Risk ratio (95% CI)		0.37 (0.19–0.74)
p-value		0.002
Grade 2, n (%)	17 (38.6)	7 (16.3)
(95% CI)	24.3–53.0	5.2–27.3
$\geq$ Grade 3, n (%)	5 (11.4)	1 (2.3)
(95% CI)	2.0–20.7	0–6.8
8 weeks		
$\geq$ Grade 2 skin toxicities, n (%)	25 (56.8)	12 (27.9%)
Risk ratio (95% CI)		0.49 (0.28–0.85)
p-value		0.006
12 weeks		
$\geq$ Grade 2 skin toxicities, n (%)	26 (59.1)	17 (39.5)
Risk ratio (95% CI)		0.67 (0.43–1.04)
p-value		0.068

Figure 1. Time to first occurrence of $\geq$ grade 2 skin toxicities. Assessments were performed by (A) investigators and (B) central review.

Table 3. Concordance rate for $\geq$ grade 2 skin toxicities in 6 weeks between investigators' assessment and central review by dermatologist in the reactive treatment group, and the pre-emptive treatment group.

Treatment group	Central review (grade)				
	0	1	2	3	Total
Investigators' assessment (grade): reactive group					
0	5 (11.4)	0	1 (2.3)	0	6 (13.6)
1	3 (6.8)	5 (11.4)	2 (4.6)	0	10 (22.7)
2	1 (2.3)	6 (13.6)	14 (31.8)	1 (2.3)	22 (50.0)
3	0	2 (4.6)	0	4 (9.1)	6 (13.6)
Total	9 (20.5)	13 (29.6)	17 (38.6)	5 (11.4)	44 [†] (100)
Investigators' assessment (grade): pre-emptive group					
0	4 (9.3)	3 (7.0)	0	0	7 (16.3)
1	10 (23.3)	13 (30.2)	4 (9.3)	0	27 (62.8)
2	0	4 (9.3)	3 (7.0)	1 (2.3)	8 (18.6)
3	0	1 (2.3)	0	0	1 (2.3)
Total	14 (32.6)	21 (48.8)	7 (16.3)	1 (2.3)	43 [†] (100)
Data are n (%).					
†The population for concordance analysis included patients for whom paired baseline and follow-up photographs were available, 87 (91.6%) out of 95 patients.					

Data are n (%).

[†]The population for concordance analysis included patients for whom paired baseline and follow-up photographs were available, 87 (91.6%) out of 95 patients.

two groups. Changes in DLQI are depicted in [Figure 2](#). There was no statistical difference in slope between the two groups ($p = 0.832$). In addition, there were no statistical differences in DLQI score for each time point ($p = 0.222$ [3 weeks], $p = 0.243$ [7 weeks] and $p = 0.874$ [13 weeks]).

Discussion

EGFR inhibitors are associated with specific skin toxicities, which can occur in a variety of types over a long duration [23], negatively impacting QOL [10]. It is important to manage skin toxicities during EGFR inhibitor treatment [17,18].

Based on current evidence, it is not clear whether race or skin color influence the occurrence and severity of skin toxicity induced by EGFR inhibitors [24–26]. The BR.21 study [26], which demonstrated the efficacy of erlotinib (an EGFR tyrosine kinase inhibitor), reported the incidence rate of rash acneiform by race (any grade: 85%, $\geq$ grade 2: 43% [Asian population]; any grade: 80%, $\geq$ grade 2: 51% [non-Asian population]). The incidence rate of any grade was similar and $\geq$ grade 2 was slightly higher in the non-Asian population [26]. Meanwhile, in the JO16565 Phase II study of erlotinib in Japan, the incidence rate of rash of any grade was 98.4% and $\geq$ grade 2 was 70.5% [27], higher than in the non-Asian population in the BR.21 study. Therefore, although it is not possible to

provide definitive comparisons between different studies, data about racial differences in skin toxicities induced by EGFR inhibitors are currently inconclusive.

STEPP was a breakthrough study which suggested that pre-emptive skin treatment could reduce the severity of skin toxicities induced by Pmab, although the study reported no data in an Asian population [19]. Despite being an open-label study, STEPP also contained no validation method such as central review. Additionally, due to awareness of adverse effects associated with the prophylactic administration of steroids [28,29], it was not popular to adopt pre-emptive skin treatment at the time our study started in Japan. To address these issues, we conducted a randomized study to assess the efficacy of pre-emptive treatment for skin toxicities induced by Pmab in the Japanese population.

In our trial, the incidence rate of $\geq$ grade 2 skin toxicities in the reactive group was 79.2% during the full observation period, similar to incidence rates reported previously [3–5], indicating the reliability of our results. No adverse effects were induced by the pre-emptive skin treatment regimen.

Pre-emptive and reactive skin treatment regimens basically followed those used in the STEPP study, with some modifications. The topical corticosteroid hydrocortisone 0.5% was used in our study (1% hydrocortisone was used in the STEPP study), because of concerns

about side effects associated with prophylactic administration of steroids, as mentioned above. Instead of doxycycline (as used in STEPP), we used minocycline, because minocycline has good tissue migration, and broad use for skin disorders, including rash acneiform, induced by anti-EGFR antibody drugs [30].

In the pre-emptive group, the decision as to whether to continue the skin treatment regimen after 8 weeks was at the discretion of each investigator. Forty out of 47 patients continued the pre-emptive skin treatment regimen, 16 of whom had $\leq$ grade 1. With the exception of patients who discontinued Pmab within 8 weeks, only three patients discontinued skin treatment after 8 weeks. During the entire 12-week skin toxicity observation period, the incidence of severe skin toxicity was less in the pre-emptive treatment group than in the reactive group, demonstrating that pre-emptive skin treatment was efficacious for not only the early phase but also over a longer time period.

Although there were no statistically significant differences in OS, PFS, TTF and ORR between treatment groups, efficacy parameters were secondary end points and, as such, the study was not large enough to be certain of detecting real differences. Nevertheless, these observations indicated that, although antitumor efficacy has been shown to be correlated with the severity of skin toxicities in some studies, pre-emptive treatment did not appear to affect the antitumor efficacy of Pmab.

We were unable to assess DLQI rigorously because of a poor questionnaire collection rate. It was assumed that, when Pmab was discontinued, patients might have had a poor Eastern Cooperative Oncology Group performance status or they transferred to a different hospital which had a palliative care unit, because anti-EGFR drugs for third-line treatment were the last line for almost all patients at the time when this study was performed, thus resulting in a poor DLQI collection rate. Nevertheless, we believe that it is important to manage skin toxicities with the objective of improving QOL because, as reported in the large trial by Naughton *et al.*, anti-EGFR therapy might lead to increased symptoms and decreased QOL induced by skin toxicities [10].

A notable point from our study was the result obtained from central review by a dermatologist in a blinded manner. To the best of our knowledge, this is the first randomized trial that has assessed the efficacy of pre-emptive treatment for Pmab with central review by a dermatologist. On the whole, the investigators tended to overestimate the severity of skin toxicities (12 [27.3%] out of 44 patients in the reactive group and 15 [34.9%] out of 43 in the pre-emptive group were assessed as having skin toxicities higher than that determined by central review). However, the proportion of underestimation was higher in the pre-emptive treatment group (8 [18.6%] out of 43 patients) than in the reactive group (4

Table 4. Adverse events.						
Adverse event	Reactive treatment (n = 48 [†]), n (%)			Pre-emptive treatment (n = 46 [†]), n (%)		
	Any grade	Grade 2	≥Grade 3	Any grade	Grade 2	≥Grade 3
Any skin toxicity:	41 (85.4)	24 (58.5)	14 (29.2)	40 (87.0)	16 (34.8)	9 (19.6)
– Rash acneiform	39 (81.3)	22 (45.8)	11 (22.9)	35 (76.1)	9 (19.6)	3 (6.5)
– Pruritus	21 (43.8)	12 (25.0)	1 (2.1)	26 (56.5)	7 (15.2)	0
– Paronychia	22 (45.8)	15 (31.3)	2 (4.2)	17 (37.0)	6 (13.0)	3 (6.5)
– Dry Skin	20 (41.7)	10 (20.8)	1 (2.1)	21 (45.7)	11 (23.9)	1 (2.2)
Nausea	6 (12.5)	0	1 (2.1)	8 (17.4)	3 (6.5)	0
Vomiting	4 (8.3)	0	0	1 (2.2)	1 (2.2)	0
Fatigue	17 (35.4)	6 (12.5)	2 (4.2)	17 (37.0)	3 (6.5)	3 (6.5)
Diarrhea	14 (29.2)	3 (6.3)	0	11 (23.9)	2 (4.3)	3 (6.5)
Neutropenia	7 (14.6)	3 (6.3)	0	13 (28.3)	3 (6.5)	9 (19.6)
Hypomagnesemia [‡]	30 (65.2)	9 (19.6)	11 (23.9)	27 (60.0)	7 (15.6)	8 (17.8)
Total number of Pmab doses	418			360		
Total Pmab doses delayed during the study	73 (17.5)			44 (12.2)		
[†] The safety population was 94 patients who were given at least one dose of Pmab.						
[‡] Magnesium level was measured in 46 out of 48 patients in the reactive treatment group and 45 out of 46 patients in the pre-emptive treatment group, respectively.						
Pmab: Panitumumab.

Figure 2. Changes in the Dermatology Life Quality Index.

†The questionnaire collection rate was 58.9% (29 out of 48 patients in the reactive group, and 27 out of 47 patients in the pre-emptive group).

DLQI: Dermatology Life Quality Index.

[9.1%] out of 44). These data suggest the possibility of bias which is a concern associated with open-label trials. Accordingly, the concordance rate between investigators' assessment and central review was 75.9%, and pre-emptive skin treatment showed statistically significant superior efficacy compared with reactive skin treatment. As for the concordance rate, it may have been difficult to score skin toxicity using CTCAE. The availability of a different scoring tool which is easier to use and simple to understand, and which corresponds to CTCAE, may facilitate decision making in daily clinical practice. In the current study, 20 patients experienced $\geq$ grade 2 skin toxicities in the pre-emptive treatment group (four of them were grade 3) during 12 weeks, suggesting that an optimized approach (with regard to pre-emptive skin treatment regimen and target patients) was considered. Some patients may need more effective skin treatment regimens,

whereas others may require no, or very little, prophylactic skin treatment.

Conclusion & future perspective

In conclusion, pre-emptive skin treatment could reduce the severity of skin toxicities during Pmab treatment. Our data provide the first evidence to clearly validate the efficacy of pre-emptive skin treatment for Pmab-associated skin toxicities in an Asian population with mCRC. Future studies are warranted to optimize pre-emptive skin treatment regimens and to target patients.

Acknowledgements

The authors thank the patients and their families for their support and participation in this trial. We are also grateful to all the investigators who participated in the study: Masahiko Koike, Hiroyuki Hisai, Sosuke Kato, Mineo Kudo and staff of the Hokkaido Gastrointestinal Cancer Study Group, especially Naoko Kataoka.

Author contributions

Conception and design: Y Kobayashi, Y Komatsu, S Yuki, H Fukushima, I Iwanaga, S Sogabe, Y Sakata, K Oba and N Sakamoto.

Administrative support: Y Sakata.

Provision of study materials or patients: Y Kobayashi, Y Komatsu, S Yuki, H Fukushima, T Sasaki, I Iwanaga, M Uebayashi, H Okuda, T Kusumi, T Miyagishima, S Sogabe, M Tateyama, K Hatanaka, Y Tsuji, M Nakamura, J Konno, F Yamamoto, M Onodera and K Iwai.

Collection and assembly of data: Y Kobayashi, Y Komatsu, S Yuki, H Fukushima, T Sasaki, M Uebayashi, H Okuda, T Kusumi, M Tateyama, J Konno, F Yamamoto, M Onodera and K Iwai.

Data analysis and interpretation: Y Kobayashi, Y Komatsu, S Yuki, H Fukushima, T Sasaki, T Miyagishima, K Hatanaka, Y Tsuji, M Nakamura, R Abe and K Oba.

Manuscript writing: Y Kobayashi, Y Komatsu, S Yuki, H F, T Sasaki, I Iwanaga, M Uebayashi, H Okuda, T Kusumi, T Miyagishima, S Sogabe, M Tateyama, K Hatanaka, Y Tsuji, M Nakamura, J Konno, F Yamamoto, M Onodera, K Iwai, Y Sakata, R Abe, K Oba and N Sakamoto.

Final approval of manuscript: Y Kobayashi, Y Komatsu, S Yuki, H Fukushima, T Sasaki, I Iwanaga, M Uebayashi, H Okuda, T Kusumi, T Miyagishima, S Sogabe, M Tateyama, K Hatanaka, Y Tsuji, M Nakamura, J Konno, F Yamamoto, M Onodera, K Iwai, Y Sakata, R Abe, K Oba and N Sakamoto.

Role of the funding source: There was no study sponsor for this trial. The Hokkaido Gastrointestinal Cancer Study Group designed and conducted the trial independently of any pharmaceutical company. The corresponding author

had full access to the data and had final responsibility for the decision to submit for publication.

Financial & competing interests disclosure

The study was funded by the Hokkaido Gastrointestinal Cancer Study Group (HGCSG), a nonprofit organization, by unrestricted donations from several pharmaceutical companies. Y Komatsu has received honoraria from Yakult Honsha, Taiho Pharmaceutical, Chugai Pharmaceutical, Merck Serono, Pfizer, Novartis, Sawai, Ono Pharmaceutical, Daiichi Sankyo and Takeda; Y Sakata has received honoraria from Yakult Honsha and Taiho Pharmaceutical. Y Komatsu has received research funding from Taiho Pharmaceutical, Lilly, Novartis, Yakult Honsha, Daiichi Sankyo, Merck Serono, Takeda and Kureha; N Sakamoto has received research funding from Mitsubishi Tanabe Pharma Corporation, Merck Sharp & Dohme, Astellas Pharma, Bristol-Myers Squibb and Chugai Pharmaceutical. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors thank David P Figgitt, Content Ed Net, for providing editorial assistance with funding from the Hokkaido Gastrointestinal Cancer Study Group.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

EXECUTIVE SUMMARY

- This randomized, open-label trial evaluated differences between pre-emptive (skin moisturizers, sunscreen, topical steroid and minocycline) and reactive (skin moisturizers only) treatment regimens for panitumumab-associated skin toxicities in 95 Japanese patients with metastatic colorectal cancer.
- The incidence of $\geq$ grade 2 skin toxicities during the 6-week treatment period (investigators' assessment) was 21.3 and 62.5% (risk ratio: 0.34; 95% CI: 0.19–0.62; $p < 0.001$) for the pre-emptive and reactive treatment groups, respectively.
- Central blinded review by an independent dermatologist showed a similar trend for pre-emptive and reactive skin treatment regimens (18.6 and 50.0%, respectively [risk ratio: 0.37; 95% CI: 0.19–0.74; $p = 0.002$]).
- The concordance rate between investigators' assessment and central review was 75.9%.
- Our results validate previous data in non-Japanese patients, indicating that pre-emptive skin treatment could reduce the severity of skin toxicities during Pmab treatment in Japanese patients with metastatic colorectal cancer.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

- 1 Foon KA, Yang XD, Weiner LM *et al.* Preclinical and clinical evaluations of ABX-EGF, a fully human anti-epidermal

growth factor receptor antibody. *Int. J. Radiat. Oncol. Biol. Phys.* 58, 984–990 (2004).

- 2 Yang XD, Jia XC, Corvalan JR, Wang P, Davis CG, Jakobovits A. Eradication of established tumors by a fully human monoclonal antibody to the epidermal growth factor receptor without concomitant chemotherapy. *Cancer Res.* 59, 1236–1243 (1999).
- 3 Van Cutsem E, Peeters M, Siena S *et al.* 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 Peeters M, Price TJ, Cervantes A *et al.* Randomized Phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J. Clin. Oncol.* 28, 4706–4713 (2010).
- 5 Douillard JY, Siena S, Cassidy J *et al.* Randomized, Phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J. Clin. Oncol.* 28, 4697–4705 (2010).
- 6 Peeters M, Balfour J, Arnold D. Review article: panitumumab – a fully human anti-EGFR monoclonal antibody for treatment of metastatic colorectal cancer. *Aliment. Pharmacol. Ther.* 28, 269–281 (2008).
- 7 Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat. Rev. Cancer* 6, 803–812 (2006).
- 8 Bouché O, Beretta GD, Alfonso PG, Geissler M. The role of anti-epidermal growth factor receptor monoclonal antibody monotherapy in the treatment of metastatic colorectal cancer. *Cancer Treat. Rev.* 36(Suppl. 1), S1–S10 (2010).
- 9 Fakih M, Vincent M. Adverse events associated with anti-EGFR therapies for the treatment of metastatic colorectal cancer. *Curr. Oncol.* 17(Suppl. 1), S18–S30 (2010).
- **Review of the safety profile, including dermatological toxicities, of the anti-EGF receptor monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.**
- 10 Naughton MJ, Schrag D, Venook AP *et al.* Quality of life (QOL) and toxicity among patients in CALGB 80405. *J. Clin. Oncol.* 31(Suppl.), Abstract 3611 (2013).
- 11 Van Cutsem E. Optimizing administration of epidermal growth factor receptor-targeted agents in the treatment of colorectal cancer. *Clin. Colorectal Cancer* 6(Suppl. 2), S60–S65 (2007).
- 12 Cunningham D, Humblet Y, Siena S *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N. Engl. J. Med.* 351, 337–345 (2004).
- 13 Peréz-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? *J. Clin. Oncol.* 23, 5235–5246 (2005).
- 14 Stintzing S, Kapaun C, Laubender RP *et al.* Prognostic value of cetuximab-related skin toxicity in metastatic colorectal cancer patients and its correlation with parameters of the epidermal growth factor receptor signal transduction pathway: results from a randomized trial of the GERMAN AIO CRC Study Group. *Int. J. Cancer* 132, 236–245 (2013).
- 15 Duvic M. EGFR inhibitor-associated acneiform folliculitis: assessment and management. *Am. J. Clin. Dermatol.* 9, 285–294 (2008).
- 16 Segal S, Tabernero J, Chosidow O *et al.* The management of skin reactions in cancer patients receiving epidermal growth factor receptor targeted therapies. *J. Dtsch. Dermatol. Ges.* 3, 599–606 (2005).
- 17 Boone SL, Rademaker A, Liu D, Pfeiffer C, Mauro DJ, Lacouture ME. Impact and management of skin toxicity associated with anti-epidermal growth factor receptor therapy: survey results. *Oncology* 72, 152–159 (2007).
- 18 Tan EH, Chan A. Evidence-based treatment options for the management of skin toxicities associated with epidermal growth factor receptor inhibitors. *Ann. Pharmacother.* 43, 1658–1666 (2009).
- 19 Lacouture ME, Mitchell EP, Piperdi B *et al.* 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).
- **Demonstrated that pre-emptive skin treatment reduced skin toxicities compared with reactive treatment among non-Asian patients with metastatic colorectal cancer receiving panitumumab.**
- 20 UMIN Clinical Trials Registry (UMIN-CTR). <https://upload.umin.ac.jp>
- 21 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. *Clin. Exp. Dermatol.* 19, 210–216 (1994).
- 22 Therasse P, Arbuck SG, Eisenhauer EA *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J. Natl Cancer Inst.* 92, 205–216 (2000).
- 23 Bianchini D, Jayanth A, Chua YJ, Cunningham D. Epidermal growth factor receptor inhibitor-related skin toxicity: mechanisms, treatment, and its potential role as a predictive marker. *Clin. Colorectal Cancer* 7, 33–43 (2008).
- **Review of the clinical presentation, predictive and prognostic value, and the management of EGF receptor inhibitor-related skin toxicity.**
- 24 Jatoi A, Green EM, Rowland KM Jr, Sargent DJ, Alberts SR. Clinical predictors of severe cetuximab-induced rash: observations from 933 patients enrolled in north central cancer treatment group study N0147. *Oncology* 77, 120–123 (2009).
- 25 Lai SE, Minnelly L, O’Keeffe P *et al.* Influence of skin color in the development of erlotinib-induced rash: a report from the SERIES clinic. *J. Clin. Oncol.* 25(Suppl.), Abstract 9127 (2007).
- 26 Wacker B, Nagrani T, Weinberg J, Witt K, Clark G, Cagnoni PJ. Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large Phase III studies. *Clin. Cancer Res.* 13, 3913–3921 (2007).
- 27 Kubota K, Nishiwaki Y, Tamura T *et al.* Efficacy and safety of erlotinib monotherapy for Japanese patients with advanced non-small-cell lung cancer: a Phase II study. *J. Thorac. Oncol.* 3, 1439–1445 (2008).
- 28 Macdonald A. Topical corticosteroid preparations. Hazards and side-effects. *Br. J. Clin. Pract.* 25, 421–425 (1971).
- 29 Purdy MJ. Adverse effects of strong topical corticosteroids. *Drugs* 8, 70–77 (1974).
- 30 Scope A, Agero AL, Duszka SW *et al.* Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J. Clin. Oncol.* 25, 5390–5396 (2007).