Prospective, observational practice survey of applied skin care and management of cetuximab-related skin reactions: PROSKIN study

Sacha I. Rothschild · Daniel Betticher · Reinhard Zenhäusern · Sandro Anchisi · Roger von Moos · Miklos Pless · Peter Moosmann · Razvan A. Popescu · Antonello Calderoni · Marco Dressler · Daniel Rauch · Stefanie Pedervita · Regina Woelky · Claudia Papet · Vera Bühler · Markus Borner

Received: 23 July 2019 / Accepted: 7 August 2019 / Published online: 23 August 2019
© The Author(s) 2019

Abstract

Purpose The study aimed to investigate strategies to prevent and treat cetuximab-induced skin reactions and their perceived effectiveness in patients with metastatic colorectal cancer (mCRC) and recurrent/metastatic squamous cell cancer of the head and neck (SCCHN).

Methods This open-label, prospective observational study was conducted in Switzerland.

Results A total of 125 patients were included (n = 91 mCRC, n = 34 SCCHN; mean age 63.3 years; 73.6% males). The frequency of acneiform rash grade ≥ 2 increased from 12.6% at week 2 to 21.7% at week 16. The proportion of patients who reported no skin reaction decreased from 75.6% at week 2 to 43.3% at week 16. The most frequently used skin products at any time of observation were moisturizing (77.6%), lipid-regenerating (56.8%) or urea-containing products (52%), systemic antibiotics (49.6%), and vitamin K1 cream (43.2%). There was no clear effectiveness pattern for all product classes: in given patients, either the product showed no effect at all or a moderate/strong effect, consistently over time.

Conclusions A great variety of low-cost general skin care products were commonly used. According to physician’s preference, systemic antibiotics and vitamin K1 cream are an appropriate approach to prevent or treat cetuximab-related skin toxicity.

Keywords Cetuximab · Observational · Practice survey · Management · Skin reactions
Introduction

Cetuximab is a chimeric monoclonal antibody that binds and inactivates the epidermal growth factor receptor (EGFR). The mechanism of blocking EGFR is an important strategy in the treatment of malignancies of epithelial origin such as colorectal cancer and squamous cell cancer of the head and neck [1, 2]. While this therapeutic approach is usually better tolerated than conventional chemotherapy, it has a unique side-effect profile related to the mechanism of action. EGFR is not solely expressed on tumor cells, but also on cells of the epidermis. Thus, skin toxicities, including rash, pruritus, dry skin, desquamation, hypertrichosis, and nail disorders, are seen in approximately 80% of patients treated with cetuximab [3–5]. Unless properly managed, these can result in dose reductions and discontinuation of treatment, in about 15–25% of patients [6–8]. The most common (90% of patients with cutaneous toxicity) and clinically most relevant skin toxicity associated with cetuximab is the papulopustular rash, also called acneiform rash [9]. Dermatologic toxicities are rarely life threatening; however, they impair quality of life (QoL) and treatment compliance. Therefore, an effective management of skin toxicities is crucial to maximize treatment efficacy and maintain QoL.

The cetuximab prescribing information states that skin reactions are very common and may require treatment interruption or discontinuation [10]. It recommends that according to clinical practice guidelines, prophylactic use of oral tetracyclines (6–8 weeks) and topical application of 1% hydrocortisone cream with moisturizer should be considered. Medium- to high-potency topical corticosteroids or oral tetracyclines have been used for the treatment of skin reactions [10, 11].

In daily clinical practice, multiple care and management options to reduce the severity of skin reactions are used, including but not limited to topical or oral antibiotics, or glucocorticosteroids. Antihistamines and local anesthetics can be administered to reduce pruritus. The frequent use of cetuximab in cancer therapy and the lack of specific clinical studies necessitate the need for studies evaluating the measures taken to alleviate skin reactions in patients treated with cetuximab.

The current observational study was initiated to gain information about the perceived effectiveness of the measures taken to alleviate skin reactions in cetuximab-treated patients. Furthermore, we aimed at assessing the impact of skin reactions on the treatment course, QoL and the reason of physicians’ choice for specific therapies.

Methods

Design

PROSKIN is a prospective observational study with a nonexperimental cohort design to provide insight into the currently used prophylactic measures and management strategies of cetuximab-related skin reactions in patients with metastatic colorectal cancer (mCRC) and or recurrent or metastatic (r/m) squamous cell cancer of head and neck (SCCHN) and the perceived effect of these strategies.

Sites

Twenty-three sites in Switzerland that were experienced in the management of tumor patients actively enrolled patients. Data collection was performed between 03 October 2012 and 30 April 2016.

Patients

Patients with mCRC or r/m SCCHN who received at least one dose of cetuximab were eligible for this study. All patients gave written informed consent prior to the study. The study was approved by local ethical committees.

The following exclusion criteria applied: (1) current radiotherapy; (2) pre-existing skin reaction (acneiform rash, dryness of skin, pustule formation, pruritus, erythema); (3) patients not willing to respond to questions from the physician; (4) patients not suitable to receive cetuximab according to the summary of product characteristics; (5) legal incapacity or limited legal capacity; (6) any psychological or medical condition that would not permit a meaningful signature of the informed consent.

In this study, the only AEs that were to be reported in the eCRF were those AEs affecting the skin. In addition, SAEs were to be reported to the Merck Global Patient Safety database, which are also reported here.

Statistical considerations

Primary data sources were the patient’s medical records and online electronic case report forms (eCRFs) completed at the time of consultation.

Descriptive statistics were provided for all continuous variables. 95% confidence intervals (CI) were provided wherever applicable. In terms of sample size, it was planned for approximately 200 patients to be documented in the study.

The Full Analysis Set (FAS) included patients diagnosed with mCRC or r/m SCCHN who received at least one cycle.
of cetuximab and data regarding skin care products and perceived effectiveness of those products were reported. The Safety Set contains all patients for whom cetuximab therapy was started.

Patients were assessed at baseline and weeks 2, 4, 6, 10 and 16. Questionnaires were completed by patients at the day of clinical visit and appointment with the treating physician at weeks 2, 4, 6, 10 and 16. The maximal observation time was 16 weeks.

The primary end point was physician’s perceived effectiveness of the skin products (skin care and medication) used.

Statistical analysis was performed using Statistical Analysis System (SAS) Version 9.1.3. (NC, USA).

Results

Patient disposition

Patient disposition is shown in Fig. 1. A total of 134 patients were enrolled.

The study stopped prematurely due to slow accrual. Of the enrolled 134 patients, 9 (6.7%) were not included in the FAS due to unknown diagnosis or a diagnosis other than mCRC or r/m SCCHN (n = 4) or no cetuximab treatment documented (n = 5). In total, 126 patients were analyzed in the Safety Set and 125 in the Full Analysis Set (FAS).

One out of the 126 experienced an adverse infusion-related reaction during the first cetuximab administration and was removed from the study. This patient was excluded from the FAS, because no data regarding skin care products and perceived effectiveness of those products were reported. While 60 patients (48.0%) completed the study (16 weeks), 65 patients (52.0%) discontinued prematurely. This was mainly due to cessation of cetuximab therapy (n = 51) or due to death (n = 6), missing information (n = 5) or withdrawal of consent (n = 3).

Demographics, baseline characteristics and planned treatment

Baseline characteristics of patients in the FAS are shown in Table 1. Mean age of patients was 63.3 ± 11.4 (range 29–84 years), and 73.6% were men. Ninety-one patients (72.8%) were diagnosed with mCRC and 34 (27.2%) with r/m SCCHN.

The Eastern Cooperative Oncology Group (ECOG) performance score of the majority of patients was either 0 (n = 61, 48.8%) or 1 (n = 54, 43.2%). Cetuximab was used as first-line treatment in 77 patients (61.6%), as second-line

Table 1  Baseline demographics and medical history

| Characteristic (FAS, N = 125) | n   | Value          |
|------------------------------|-----|----------------|
| Demographics                 |     |                |
| Age, mean ± SD, years        | 125 | 63.3 ± 11.4    |
| Min; Max                     |     | 29; 84         |
| Sex, males, %                | 92  | 73.6           |
| Females, %                   | 33  | 26.4           |
| Body surface area, m²        | 125 | 1.80 ± 0.20    |
| Medical history              |     |                |
| Metastatic colorectal cancer | 91  | 72.8           |
| Recurrent/metastatic squamous cell cancer of the head and neck | 34 | 27.2 |
| ECOG performance score       |     |                |
| 0                            | 61  | 48.8           |
| 1                            | 54  | 43.2           |
| 2                            | 10  | 8.0            |
| 3                            | 0   | 0.0            |
| 4                            | 0   | 0.0            |
| Missing                      | 0   | 0.0            |
| Previous anti-cancer treatmenta |     |                |
| Surgery                      | 75  | 60.0           |
| Chemotherapy                 | 58  | 46.4           |
| Radiotherapy                 | 34  | 27.2           |
| Biologic                     | 19  | 15.2           |
| None                         | 23  | 18.4           |

FAS Full Analysis Set, SD standard deviation

aMultiple responses were present in the data per patients
treatment in 31 patients (24.8%), as third-line in 13 patients (10.4%) and later lines in 3 patients (2.4%).

**Prophylaxis and treatment**

Table 2 lists the skin products used (skin care products and medications administered to treat or prevent skin reactions) at any time during the study. The most frequently used skin products were moisturizing agents (97 patients, 77.6%), lipid-regenerating products (71 patients, 56.8%), urea-containing products (65 patients, 52.0%), systemic antibiotics (62 patients, 49.6%) and vitamin K1 cream (54 patients, 43.2%).

Other medications included topical steroids, antiseptic products, wet wraps, other topical treatments, topical antibiotics, other systemic treatments, topical antibiotics plus topical steroids combined in one product. These products were used in less than 30% of patients.

Systemic steroids (28% of patients) and systemic antihistamines (28% of patients) were used as pre-medications prior to cetuximab infusions, and as treatment of infusion-related reactions.

**Effectiveness**

**Categorical effectiveness**

The perceived effectiveness of the skin products (primary end point) is summarized for the most frequently administered agents at weeks 2, 6 and 16 in Fig. 2.

For all drug classes, effectiveness ratings varied across patients: “no effect” and “moderate”/“strong” were the preferred ratings of physicians and the two peaks stayed over the time. “Weak” or “very strong” was rarely mentioned. For example, “moderate” to “very strong” effectiveness was perceived by a majority of physicians in patients who received systemic antibiotics at week 2 (57.2% of 35 patients treated) and at week 6 (62.2% of 45 patients treated). This frequency remained at the same level until week 16 (60.7% in 28 patients treated by week 16). Overall, the percentages of responses “no effect” lowered and “moderate” gained percentages over time.

**Mean effectiveness across visits**

On calculation of the average numerical effectiveness values (from 0 = no, to 4 = very strong) of the assessments across all visits for each patient and for each type of medication, mean perceived effectiveness (regardless of prophylactic or reactive usage) was highest for the combination of topical antibiotics and steroids (1.95 ± 1.16 in 14 patients), followed by systemic antibiotics (1.40 ± 1.10 in 62 patients) and vitamin K1 cream (1.25 ± 0.87 in 54 patients, Fig. 3). Lowest mean effectiveness values were observed for antiseptic products (0.67 ± 0.98 in 26 patients) and lipid-regenerating products (0.83 ± 1.00 in 71 patients), respectively.

The average values for reported pre-medications, regardless of prophylactic or reactive usage was highest for antihistamines (1.81 ± 1.36 in 36 patients), followed by systemic steroids (1.72 ± 1.37 in 28 patients).

**Impact of skin reactions on the course of therapy**

No relevant differences, in the cetuximab dose (mg/m²) or the percentage of dose delays, were observed between patients who had the first occurrence of skin reactions early (i.e., at week 2, 4 or 6) in comparison to those with a first occurrence at later time points (weeks 10 or 16), or without any skin reaction. This was also the case for the first occurrence of skin reactions grade ≥ 2 or for the first occurrence of acneiform rash (both any grade and grade ≥ 2).

### Table 2 Use of skin care products and medications

| Planned treatment (FAS, N = 125) | n    | %    | Prophylactic | Reactive |
|----------------------------------|------|------|--------------|----------|
| Moisturizing products            | 97   | 77.6 | 82           | 33       |
| Lipid-regenerating products      | 71   | 56.8 | 51           | 24       |
| Urea-containing products         | 65   | 52.0 | 57           | 20       |
| Systemic antibiotics             | 62   | 49.6 | 35           | 32       |
| Vitamin K1 cream                 | 54   | 43.2 | 42           | 25       |
| Systemic antihistamines          | 36   | 28.8 | 30           | 5        |
| Systemic steroids                | 28   | 22.4 | 23           | 3        |
| Topical steroids aseptic products| In about 25% | In 4–12% | In about 25% | In 4–12% |

**FAS Full Analysis Set**

 Springer
Patient’ impressions of skin reactions: itching intensity

A majority of the patients experienced ‘no itching’ at any time, i.e., 75.6% at week 2, 53.6% at week 4, 55.9% at week 6, 54.9% at week 10 and 53.3% at week 16. Strong or very strong intensity was reported in very few patients (3.4% at week 2, 1.0% at week 6 and none at week 16).

Impact on daily life

At week 2, 75.6% patients reported no impact of skin reactions on daily life. Thereafter the proportion of patients with no impact decreased to 57.1% at week 4, 52.9% at week 6, 41.5% at week 10 and 43.3% at week 16. Very strong impact on daily life was reported by very few patients (1.7% at week 2, 1.0% at week 6 and 1.7% at week 16).

Influence on willingness to continue therapy

A majority of the patients reported no influence of skin reactions on their willingness to continue therapy and the proportion of patients remained almost identical at all weeks (68.9% at week 2, 67.0% at week 4, 66.7% at week 6, 64.6% at week 10, and 63.3% at week 16).

A majority of the patients reported no influence of skin reactions on their willingness to continue therapy and the proportion of patients remained almost identical at all weeks (68.9% at week 2, 67.0% at week 4, 66.7% at week 6, 64.6% at week 10, and 63.3% at week 16).

At week 2, 21.0% of patients strongly favoured continuation of therapy. Thereafter, the proportion of patients slightly increased to 24.1% at week 4, 24.5% at week 6, 25.6% at week 10 and 28.3% at week 16. Very few patients (0.8% at week 2; 0.9% at week 4; 0% at weeks 6 and 10; 1.7% at week 16) strongly favoured discontinuation of therapy.

Perceptions of the measures taken are summarized in Fig. 4.

Acceptance of measures

At week 2, 36.1% patients perceived the measures taken, against skin reactions, to be neutral, which slightly decreased thereafter (32.1% at week 4, 29.4% at week 6, 26.8% at week 10, and 26.7% by week 16). A similar proportion of patients at all weeks (28.6% at week 2, 33.0%
at week 4, 32.4% at week 6, 32.9% at week 10, and 31.7% at week 16) ‘very much accepted’ the measures taken. Very few patients found the measures taken, against skin reactions, as very annoying (0.0% at week 2, 2.7% at week 4, 1.0% at week 6, 2.4% at week 10 and 3.3% at week 16).

**Effect of skin care measures and medication on skin reactions**

A majority of the patients reported no impact of skin care measures and medication on skin reactions at week 2 (62.2%). Thereafter, the proportion of patients with no impact decreased to 34.8% at week 4, 30.4% at week 6, 24.4% at week 10 and 23.3% at week 16. At week 6 and thereafter, a majority of patients reported a better than weak efficiency (53% at week 6, 58.5% at week 10 and 58.3% at week 16).

**Change of skin reaction**

A majority of the patients reported no change in the skin reaction at week 2 (69.7%). The proportion of patients reduced to 43.8% at week 4 and showed an increasing trend in later weeks (51.0% at week 6, 54.9% at week 10 and 68.3% at week 16). Only 1.7% patients at week 2 perceived an improvement in skin reactions. The proportion of patients increased to 12.5% at week 4, 24.5% at week 6 and later decreased to 15.9% patients at week 10. By 16 weeks, 16.7% patients perceived an improvement in skin reactions.

**Safety**

**Skin reactions incidence and grading**

Acneiform rash occurred in 94 patients (74.6%), dryness of skin in 78 (61.9%), pruritus in 56 (44.4%), paronychia in 21 (16.7%) and erythema in 47 (37.3%). The majority of these reactions were grade 1 and to a lesser extent grade 2. There were no grade 4 reactions. Only one serious adverse event was reported as related to the skin (acneiform rash). In this case, rash, dyspnea, tachycardia and nausea occurred during the first infusion and were rated as IRR.

**Premature discontinuations**

The primary reasons for premature cessation of the study as reported for 65 patients were discontinuation of cetuximab (51 cases), patient death (6 cases) and withdrawn consent (3 cases). The cause of death in five patients was the outcome of one or more SAEs, two of which were disease progression; the cause of death for one patient was unknown. The dropout information was missing in 5 patients. Cessation of cetuximab therapy was related to skin reactions in five patients (4.0% of 125 patients treated).

**Serious adverse events**

During the course of the study, there were 26 SAEs (excluding two events of disease progression) in 16 Individual Case Safety Reports (ICSR). Four of these 16 ICSRs reported 6 SAEs with a fatal outcome: pneumonia in 1 ICSR, gastric hemorrhage and vascular injury in 1 ICSR, infection in 1 ICSR, ischemic colitis and infectious colitis in 1 ICSR. The remaining 12 ICSRs reported 20 SAEs: rash, dyspnea, tachycardia and nausea in 1 ICSR (all events occurred during the first infusion and were regarded as IRR), fall, femoral neck fracture, foot fracture in 1 ICSR, nausea, vomiting, diarrhea and dehydration in 1 ICSR, hypersensitivity in 2 ICSRs, infusion-related reaction, anaphylactic shock, device-related infection, renal failure, deep vein thrombosis, dysphagia and diarrhea in 1 ICSR each.
Discussion

The optimal approach on how to prevent and manage the cutaneous side effects of cetuximab and other EGFR-targeting antibodies has not been clearly established. The prospective observational PROSKIN study provides detailed insights into current preventive measures and treatment of skin reactions related to cetuximab in Switzerland. The study included patients from 23 sites in the country including university hospitals, secondary- and primary-level hospitals and oncological practices, therefore reflecting the full spectrum of oncological patient care in the country. The study demonstrates a broad variety of preventive and therapeutic skin care that is used in patients undergoing cetuximab therapy. Each patient receives on average three products at the same time. The most frequently used products in this study were moisturizing, lipid-regenerating and urea-containing products (i.e., no typical pharmaceutical products), followed by systemic antibiotics and vitamin K1 cream. Thus, physicians mainly used low-cost topical products.

Moderate to very strong effectiveness was perceived by a majority of physicians for patients who received systemic antibiotics or vitamin K1 cream, while moisturizing, lipid-regenerating and urea-containing products were perceived as less effective. An interesting finding was that a specific pattern in effectiveness was observed for all product classes over the whole time of the study: either the product showed no effect at all or a moderate/strong effect. No product class appeared to be substantially superior to the others on an individual patient level. We therefore conclude that the best treatment option needs to be explored individually.

Only one in five patients received systemic antibiotics as primary prophylaxis from the beginning, so this drug class is often reserved for treatment-associated adverse events or as secondary prophylaxis. As expected, the frequency of acneiform rash grade ≥ 2 increased during the treatment course, from 12.6% at week 2 to 21.7% at week 16. These numbers are reassuring in the sense that the majority of patients did not develop severe skin reactions. Nevertheless, the proportion of patients whose skin reactions did impact on daily life steadily increased during treatment, reaching 76.7% at week 16. In line with this observation, the reactive use of all products tended to increase during the treatment course. These findings underline the importance of assessing not only severe toxicities, as also mild or moderate toxicities might affect QoL and patients’ daily life. The toxicity rates confirm published data from prospective clinical trials investigating cetuximab in patients with mCRC and r/m SCCHN.

The results of our study need to be discussed in the context of prior studies investigating different approaches of skin toxicity management in patients treated with cetuximab. In a US-American monocenter randomized controlled trial on 48 patients, prophylaxis with oral minocycline decreased the severity of acneiform rash during the first month of cetuximab treatment, while topical tazarotene was associated with significant irritation [12]. In the same institution, a prospective randomized trial of topical pimecrolimus for cetuximab-associated acne-like eruption in 24 patients failed to show clinically meaningful benefit [13]. Conversely, in a case series of 20 patients treated with different epidermal growth factor receptor inhibitors in Greece, pimecrolimus cream 1% (substituted by metronidazole 1% cream) was effective in most patients (> 50% reduction of erythema, pustules and pruritus) [14]. Minocycline was used in seven patients in the PROSKIN study, none was treated with topical tazarotene or pimecrolimus. In a study with historical controls as comparator, in 40 patients, cetuximab prophylaxis with topical vitamin K1 cream did not translate into clinically meaningful benefit in terms of reducing acneiform rash [15]. However, an Italian monocenter study of 41 patients with metastatic colorectal cancer treated with cetuximab suggested a possible benefit of topical vitamin K1-based cream as prophylaxis for skin rash [16]. In our PROSKIN study, most physicians perceived a moderate effect of topical vitamin K1 cream.

Ocvirk et al. reported on a group of 31 patients with acne-like rash, who, after the first documented cutaneous toxicity, received topical use of emollients. Patients with grade 2 rash received emollients and topical antibiotics. Patients developing grade 3 rash discontinued therapy with cetuximab until recovery and were treated with emollients, topical and systemic antibiotics. Of 31 patients, six had grade 3 rash, 16 patients grade 2 and nine patients grade 1 acne-like rash [17]. As in our study, no grade 4 skin reactions were observed.

A multicenter observational study in 55 patients reported delayed occurrence and milder course of skin reactions with the use of a pre-defined prophylactic skin care regimen including vitamin K1 ointment and oral doxycycline [17].

Overall, similar to our findings, results from previous studies show conflicting results and could so far not establish an evidence-based prophylaxis or treatment regimen for cetuximab-related skin toxicities. Nevertheless, the topic was discussed at consensus meetings and recommendations have been published [18, 19]. Another relevant factor is the low rate of consensus between oncologists and dermatologists in labeling and grading of skin reactions and the frequent interobserver variability [20].

A number of limitations and strengths of the study design need to be considered when discussing the results of this study. The study was small, had no control arm and was unblinded and thus should be considered as real-world observational study with focus on skin products used and
their perceived effectiveness over time. In many subgroups, the number of patients was small and therefore results have to be carefully interpreted. There was a high rate of patients that were lost to follow-up. All patients came from Switzerland which had advantages in terms of the access of patients to products and uniform procedures, but might limit the generalizability of the findings to patients in other health-care settings and countries. It was the clinical decision of the respective treating physicians to assign selected patients to certain therapies and not to other available treatment options that potentially may introduce allocation or channeling bias and confound the association between treatment and outcomes [21]. However, this is an advantage as physicians already have some experience with the regimen they use. With a pre-defined regimen, there would be a learning curve at the beginning and possible skepticism that could influence how physicians perceive the effectiveness. Physicians and patients willing to participate in non-interventional studies such as ours may be particularly motivated or interested in science and therefore also be patient to selection bias. Finally, the follow-up period of 16 weeks was relatively short. However, it has been shown that skin toxicities usually develop within the first few weeks of cetuximab therapy. Therefore, we defined this time window. Moreover, at week 16 a large proportion of patients show tumor progression and these patients have to be discontinued from the study introducing another potential selection bias.

Conclusions

In conclusion, in Switzerland oncologists used a great variety of low-cost general skin care products for the prevention or treatment of cetuximab-related skin toxicity in patients with mCRC or r/m SCCHN. They gave preference to systemic antibiotics and vitamin K1 cream. Patients perceived overall “moderate” efficacy of the various measures. For most patients, skin reactions did not influence their willingness to continue cetuximab therapy.

Availability of data and material The datasets generated and/or analyzed during the current study are not publicly available as sharing is not explicitly covered by patient consent. Medical History (FAS) N=125

Compliance with ethical standards

Conflict of interest The study was funded by Merck (Switzerland) AG, Zug, an affiliate of Merck KGaA, Darmstadt, Germany. SIR has received honoraria for advisory boards (paid to the institution) from Merck and research funding from Merck. RVM has participated in advisory boards of Merck and Amgen and received speaker honoraria from Amgen and Merck. PM has participated in an advisory board of Merck. VB is a full-time employee at Merck (Switzerland) AG, Zug. The other authors declare no competing interests. The authors confirm they have full control of all primary data and agree to allow the journal to review their data if requested.

Ethical considerations This study was conducted in accordance with the protocol, the ethical principles laid down in the Declaration of Helsinki, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice (ICH GCP), guidelines and applicable regulatory requirements. The protocol, ICF, any other materials provided to the patients, and further requested information were submitted to the IEC/IRB and the competent authority. The regulatory application or submission for regulatory approval was made by the sponsor or designee as required by national law. The competent authority and the IEC/IRB were notified of the end of the study in accordance with local regulations.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Frampton JE (2010) Cetuximab: a review of its use in squamous cell carcinoma of the head and neck. Drugs 70(15):1987–2010
2. Guggina LM, Choi AW, Choi JN (2017) EGFR inhibitors and cutaneous complications: a practical approach to management. Oncol Ther 5(2):135–148
3. Bonomo P, Loi M, Desideri I et al (2017) Incidence of skin toxicity in squamous cell carcinoma of the head and neck treated with radiotherapy and cetuximab: a systematic review. Crit Rev Oncol Hematol 120:98–110
4. Petrelli F, Borgonovo K, Barni S (2013) The predictive role of skin rash with cetuximab and panitumumab in colorectal cancer patients: a systematic review and meta-analysis of published trials. Target Oncol 8(3):173–181
5. Su X, Lacouture ME, Jia Y, Wu S (2009) Risk of high-grade skin rash in cancer patients treated with cetuximab—an antibody against epidermal growth factor receptor: systemic review and meta-analysis. Oncology 77(2):124–133
6. Van Cutsem E, Kohne CH, Hitre E et al (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 360(14):1408–1417

Author contributions Conception/design: PD Dr. med. Dr. phil. nat. SR, University Hospital Basel, Switzerland and Merck (Switzerland) AG, Zug, an affiliate of Merck KGaA, Darmstadt, Germany. Editorial support by Prof. DP, 3P Consulting, Seefeld, Germany and Merck (Switzerland) AG, Zug, an affiliate of Merck KGaA, Darmstadt, Germany. Collection and/or assembly of data: Unidata AG, Vienna, Austria, was responsible for the operational aspects of the study’s EDC system. Data management, data analysis, biostatistics and medical writing services were performed by MakroCare Clinical Research Limited. India. Data analysis and interpretation: all authors. Final approval of manuscript: all authors.

Funding The study is funded by Merck (Switzerland) AG, Zug, an affiliate of Merck KGaA, Darmstadt, Germany.
7. Vermorken JB, Mesia R, Rivera F et al (2008) Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 359(11):1116–1127

8. Heinemann V, von Weikersthal LF, Decker T et al (2014) FOL-FIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 15(10):1065–1075

9. Jaka A, Gutierrez-Rivera A, Lopez-Pestana A et al (2015) Predictors of tumor response to cetuximab and panitumumab in 116 patients and a review of approaches to managing skin toxicity. Actas Dermo-Sifiliograficas 106(6):483–492

10. European Agency for the Evaluation of Medicinal Products (EMA) Erbitux (Cetuximab) Summary of Product Characteristics (SmPC). June 2014. http://www.ema.europa.eu. Accessed 30 May 2018

11. Lacouture ME, Anadkat MJ, Bensadoun RJ et al (2011) Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer 19(8):1079–1095

12. Scope A, Agero AL, Dusza SW et al (2007) Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. J Clin Oncol 25(34):5390–5396

13. Scope A, Lieb JA, Dusza SW, Phelan DL, Myskowski PL, Saltz L, Halpern AC (2009) A prospective randomized trial of topical pimecrolimus for cetuximab-associated acnelike eruption. J Am Acad Dermatol 61(4):614–620

14. Nikolaou V, Stratigos A, Antoniou C, Kiagia M, Nikolaou C, Katsambas A, Syrigos K (2010) Pimecrolimus cream 1% for the treatment of papulopustular eruption related to epidermal growth factor receptor inhibitors: a case series and a literature review of therapeutic approaches. Dermatology 220(3):243–248

15. Jo JC, Hong YS, Kim KP et al (2013) Topical vitamin K1 may not be effective in preventing acneiform rash during cetuximab treatment in patients with metastatic colorectal cancer. Eur J Dermatol EJD 23(1):77–82

16. Pinta F, Ponzetti A, Spadi R et al (2014) Pilot clinical trial on the efficacy of prophylactic use of vitamin K1-based cream (Vigorskin) to prevent cetuximab-induced skin rash in patients with metastatic colorectal cancer. Clin Colorectal Cancer 13(1):62–67

17. Ocvirk J, Cencelj S (2010) Management of cutaneous side-effects of cetuximab therapy in patients with metastatic colorectal cancer. J Eur Acad Dermatol Venereol 24(4):453–459

18. Pinto C, Barone CA, Girolomoni G, Russi EG, Merlano MC, Ferrari D, Maiello E (2011) Management of skin toxicity associated with cetuximab treatment in combination with chemotherapy or radiotherapy. Oncologist 16(2):228–238

19. Pinto C, Barone CA, Girolomoni G, Russi EG, Merlano MC, Ferrari D, Maiello E (2016) Management of skin reactions during cetuximab treatment in association with chemotherapy or radiotherapy: update of the italian expert recommendations. Am J Clin Oncol 39(4):407–415

20. Duffour J, Thezenas S, Dereure O et al (2010) Inter-observer agreement between dermatologists and oncologists in assessing dermatological toxicities in patients with metastatic colorectal cancer treated by cetuximab-based chemotherapies: a pilot comparative study. Eur J Cancer 46(18):3169–3174

21. Delgado-Rodriguez M, Llorca J (2004) Bias. J Epidemiol Community Health 58(8):635–641

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.