# Assessment of Skin-related Toxicity in Patients with Metastatic Colorectal Cancer Treated with Cetuximab

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**SUMMARY** Monoclonal antibodies (mAbs) blocking the epidermal growth factor receptor (EGFR) pathway, such as cetuximab, have been widely used in recent years for the treatment of metastatic colorectal cancer (mCRC). The purpose of this study was to evaluate the profile of the side effects of cetuximab affecting the skin and its appendages. We gathered the medical records on skin-related toxicity in 46 patients treated with cetuximab for mCRC in the Department of Clinical Oncology, University Hospital in Krakow in 2009-2013. Skin toxicity was classified according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0. The typical side effects of cetuximab were observed. The most common skin toxicity was an acne-like skin rash (80% of patients) and paronychia (20%). Other side effects were trichomegaly, hypertrichosis, and allergic reactions.

In view of high incidence of skin lesions during treatment with cetuximab, it is essential to observe patients carefully and to control the side effects during therapy. Previous experience from clinical trials shows that in some cases proper care and prevention can improve the quality of the patients' lives.

**KEY WORDS**: cetuximab, EGFR, *K-ras,* metastatic colorectal cancer, rush, skin toxicity

## INTRODUCTION

Colorectal cancer (CRC) is one of the most frequently diagnosed malignancies in both men and women (1). One of the treatment options for metastatic CRC (mCRC) is targeted therapy directed against the epidermal growth factor receptor (EGFR). This includes monoclonal antibodies (mAbs) – cetuximab and panitumumab. Cetuximab has shown its effectiveness in various lines of treatment of mCRC both in combination with cytotoxic chemotherapy and in monotherapy, mainly in patients with the wildtype *K-ras* gene. Thus, mutation of *K-ras* is thought to be a negative predictive factor for the treatment

with this mAb. Recently published combined analysis of pooled individual patient data from randomized phase III CRYSTAL (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) and randomized phase II OPUS (Oxaliplatin and Cetuximab in First-Line Treatment of mCRC) clinical trials demonstrated that addition of cetuximab to standard first-line chemotherapy in patients with *K-ras* wild-type mCRC significantly improved overall survival (OS) (hazard ratio [HR] 0.81; *P*=0.0062), progression-free survival (PFS) (HR 0.66; *P*<0.001) and overall response rate (ORR) (odds ratio 2.16;

*P*<0.0001) (2). The randomized CO.17 trial comparing cetuximab monotherapy versus best supportive care (BSC) in mCRC after failure of standard chemotherapy containing oxaliplatin, irinotecan, and 5-fluorouracil showed that cetuximab significantly improves OS, PFS and ORR (3). Finally, the BOND trial (4) demonstrated that addition of cetuximab to irinotecan after failure of irinotecan-based chemotherapy in the previous setting significantly improved PFS and ORR compared to treatment with cetuximab alone. It is noteworthy that the efficacy of cetuximab shown in these trials was significantly higher among patients with prominent skin rash after cetuximab compared to patients without any or with mild skin reactions.

Upregulated EGFR may cause uncontrolled changes in cell cycles. Overexpression of EGFR is also associated with increased metastatic potential and poorer prognosis in numerous malignancies (5,6). EGFR, also known as human epidermal growth factor receptor 1 (HER-1), is a member of HER family of receptors. They are transmembrane glycoproteins and consist of three main components: the extracellular ligand binding domain, transmembrane part, and conserved intracellular tyrosine kinase (5). After binding of an extracellular domain to its ligand, the tyrosine kinase is activated and starts to phosphorylate subsequent kinases on a signaling pathway. One of such networks is the mitogen-activated protein kinase pathway (MAPK). The elements of the axis and the effects of its blockage by cetuximab are shown in Figure 1. As a result of the activation of the pathway, changes in cell behavior such as enhanced proliferation, transformation and impaired apoptosis, or differentiation are seen. Moreover, signaling networks allow the signal to be amplified on its way from the cell membrane to the nucleus (7). Inhibition of the EGFR/ *K-ras* pathway in mCRC is connected with adverse effects, among them: skin toxicity, diarrhea, hypomagnesemia, and infusion reactions, as well as the most dangerous one – anaphylaxis. Taking into account the toxicity involving the skin and appendages, the most frequent problems are: multiform rashes, especially acneiform, paronychia with pyogenic granuloma, xerosis, eczema, hair changes, hypertrichosis, fissures, and hyperpigmentation (8).

The purpose of this study was to evaluate the profile of the side effects of cetuximab affecting the skin and its appendages.

## MATERIALS AND METHODS

### Study group

A retrospective analysis of 46 patient histories was conducted (from October 2009 to March 2013). To be
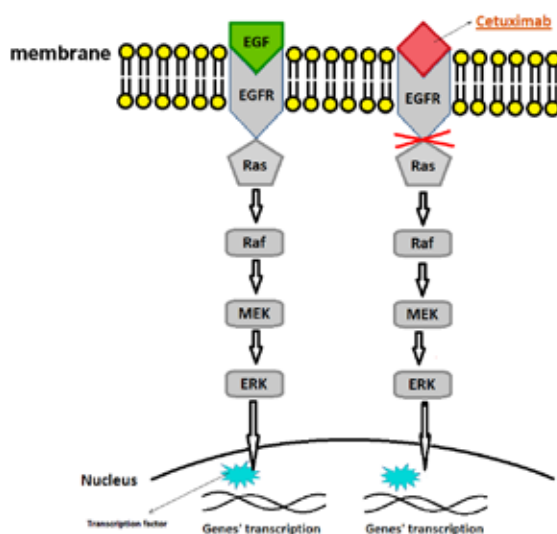


**Figure 1. EGFR** signaling axis and the effects of cetuximab blockage (7).

included in the analysis, a patient had to be treated using cetuximab in the Department of Clinical Oncology, University Hospital in Krakow, Poland. Additional inclusion criteria were: age 18 and above, histologically confirmed diagnosis of CRC, presence of metastatic disease in diagnostic imaging (including computer tomography, magnetic resonance imaging, positron emission tomography or bone scintigraphy), and lack of *K-ras* mutation. The exclusion criteria were: past or present concurrent malignancies, lack of consent to participate in the study, and previously diagnosed skin disease requiring chronic dermatological treatment.

Factors taken into consideration during the analysis included: sociodemographic data, localization of primary cancer, clinical stage of the tumor according to the TNM staging system, type of treatment received, side effects related to cetuximab therapy and their intensity, and the status of *K-ras* mutation. Skin toxicity was classified according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0 (CTCAE v 4.0) (9) as shown in Table 1.

Additionally, after receiving the patient's permission, photographic documentation of the skin changes was made.

### Statistical evaluation

Statistical analysis was conducted using computer software Statistica 11.0 PL by StatSoft Poland (licensed to the Jagiellonian University Medical College, Poland). Descriptive statistics (range, mean, standard deviation, percentage distribution) were used.

Student's t-test was used when comparing quantitative variables, and the Mann-Whitney test was used

**Table 1.** Grades of chosen skin-related side effects according to CTCAE v. 4.0 (9)

| Adverse Event | Grade | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| **Acneiform rash** | Lesions on < 10% of BSA. | Lesions on 10-30% of BSA.<br><br>Associated with psychological impact. Affecting instrumental ADL. | Lesions on > 30% of BSA.<br><br>Limiting self-care ADL. Local superinfection.<br><br>Oral antibiotics indicated. | Lesions on any of BSA. Extensive superinfection. Intravenous antibiotic indicated.<br><br>Life-threatening consequences. | Death |
| **Paronychia** | Edema or erythema of the nail fold, cuticle disruption. | Edema or erythema of the nail fold with pain, discharge or nail plate separation, affecting instrumental ADL*.<br><br>Oral or localized intervention indicated. | Limiting self care ADL.<br><br>Surgical intervention or intravenous antibiotics needed. | - | - |
| **Hypertichosis** | Longer and thicker hair which the patient can manage with periodic shaving and removal of hairs. | Longer and thicker hair on exposed area of the body. Frequent shaving or destructive methods to remove hair required. Psychological impact present. | - | - | - |
| **Pruritus** | Mild or localized. Topical intervention needed. | Intense or widespread. Intermittent. Skin changes caused by scratching.<br><br>Limiting instrumental ADL.<br><br>Oral intervention needed. | Intense or widespread. Constant.<br><br>Limiting self care ADL or sleep.<br><br>Oral corticosteroid or immunosuppressive drugs needed. | - | - |

ADL – Activities of daily living
BSA – Body surface area
*In some cases patients had more than one localization of metastatic disease.

in the absence of a normal distribution of factors. Chi-squared test was used when comparing qualitative variables, and the R Spearman test was applied for examining the correlation between quantitative variables. The results were presented using odds ratios (OR).

A *P*-value <0.05 was taken to indicate significance.

### Ethical approval

The protocol of this study was approved by the Jagiellonian University Medical College Ethical Committee (registry number KB/254/B/2011). The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

## RESULTS

Forty-six patients were included in the study. The population consisted of 12 women and 34 men; the median age was 55.4 years. The demographic distribution is shown in Table 2.

All the patients were treated with cetuximab as a palliative therapy. Cetuximab was administered in a standard dose – 400 mg/m$^2$ in a first dose and 250 mg/m$^2$ in each subsequent dose.

The most commonly encountered adverse event, in both cetuximab in monotherapy and connected with chemotherapy, was an acne-like skin rash (observed in 80% of patients, n=37), predominantly on the head and upper torso (59.5%, n=22 and 37.8%, n=14). Multiform rashes occurred mainly in the G2 stage (51.4%, n=19) according to CTCAE v 4.0 (9). In

**Figure 2.** The typical course of a rash.

a) Papulopustular rash

b) Papulopustular rash with crusts

c) and d) Erythema and telagiectases

8.1% (n=3) they occurred in the G3 stage. However, all these patients completed chemotherapy treatment of over 30 cetuximab doses. The rash was characterized by a typical clinical course. Usually, after 2-4 weeks a typical papulopustular rash could be seen. Changes were resolved by crusting. In some cases, in areas where lesions occurred, persistent dry skin, erythema, or telangiectases could be observed.

Another manifestation of cetuximab cutaneous toxicity was paronychial cracking starting typically 2-3 months after initiation of the therapy. These lesions occurred either on the fingers or toes and were reported in 20% (n=9) of patients. Because of the development of G3 toxicity (according to CTCAE v. 4.0) (9) one patient stopped cetuximab therapy. Less common side effects such as hypertrichosis and itching were observed in individual patients.

In 3 patients (6.5%) severe anaphylactic reactions to cetuximab developed and manifested as erythema, sweating, dyspnea, tachycardia, and hypotension. The treatment was discontinued. In our study, serum sickness appeared in one case. There were no treatment-related deaths.

The median duration of treatment was 17 weeks (range 1 to 64). There were several chemotherapy protocol types: cetuximab in monotherapy or in combination with chemotherapy based on irinotecan, oxaliplatin, or capecytabine. Regardless of cetuximab treatment type, the progressive diseases (PD, based on imaginary studies or symptomatic progression) were principal reasons for cessation of treatment (80.4%, n=37).

**Table 2.** Baseline demographic, disease and chemotherapy characteristics

| Parameter | No. | % |
|---|---|---|
| Age (years) | | |
| Median | 55.4 | - |
| Range | 26-78 | - |
| Sex | | |
| Men | 34 | 74 |
| Women | 12 | 26 |
| Site of primary cancer | | |
| Rectum | 18 | 39 |
| Sigmoid colon | 18 | 39 |
| Rectum + sigmoid colon | 5 | 11 |
| Transverse colon + hepatic and/or splenic flexures | 3 | 7 |
| Ascending colon | 1 | 2 |
| Cecum | 1 | 2 |
| No. of metastatic sites (organs involved) | | |
| <=1 | 37 | 78.3 |
| >1 | 9 | 19.6 |
| Site of metastases | | |
| Liver | 35 | 76.1 |
| Lungs | 10 | 21.7 |
| Peritoneum | 5 | 10.9 |
| Ovaries | 2 | 4.3 |
| Bones | 2 | 4.3 |
| Urinary bladder | 1 | 2.2 |
| Treatment line | | |
| 1 | 13 | 28.3 |
| 2 | 15 | 32.6 |
| 3 | 12 | 26.1 |
| ≥4 | 6 | 13 |
| Cetuximab | | |
| Number of cetuximab doses | | |
| 1 | 3 | 6.5 |
| 2-5 | 3 | 6.5 |
| 6-10 | 12 | 26.1 |
| 11-15 | 9 | 19.6 |
| 16-20 | 5 | 10.9 |
| >20 | 12 | 26.1 |
| Lack of data | 2 | 4.3 |
| | | |
| Type of therapy | | |
| Monotherapy | 5 | 10.9 |
| Chemoimmunotherapy (combination therapy) | 41 | 89.1 |
| | | |
| Reason for treatment ending | | |
| Progression | 37 | 80.1 |
| Intolerance (including allergic reactions) | 5 | 10.9 |
| Decision of an oncologist | 1 | 2.2 |
| Lack of data | 3 | 6.5 |

**Figure 3.** Periungueal changes.

Because of skin toxicity, the treatment was temporary interrupted in four patients and ended in the one above-mentioned case.

In our study there was no statistically significant association between the presence of a rash (no rash vs. any rash) and factors such as gender, age (>=55 years old vs. <55), location of the primary tumor (rectum vs. any other part of the colon), and number (>1 vs. >=1) and location (liver vs. other places) of metastases.

## DISCUSSION

Targeted therapy is becoming an increasingly popular treatment option for cancer. One of advantages of targeted agents is decreased risk of severe systemic side effects compared to cytotoxic agents. It is worth noting that adverse effects, while less dangerous, are common and should be treated early. In many cases, proper care and prevention allow the quality of patient's life to be improved (10). In this study, a cetuximab-dependent skin toxicity profile was described. Our results are generally consistent with the data presented in other studies (Table 3).

The most common skin manifestation in the analyzed population was an acneiform eruption – 80%. Figure 2 shows the typical clinical course of the rash (a-d). Rash is the most frequently mentioned side ef-



**Figure 4.** Trichomegaly.

fect during cetuximab therapy. In the literature, the fluctuation in the incidence oscillates from 52 to 92% (3,11-15). The main mechanism of acne-like rash is not fully understood. The blockage of EGFR both by monoclonal antibodies and EGFR-specific tyrosine inhibitors may result in similar skin toxicity (16). The EGFR is expressed in the basal epidermis layer and is indicated as an important factor in survival, motility and differentiation of keratinocytes (17). This can explain skin toxicity occurring during treatment with cetuximab, but does not clarify the acneiform nature of this eruption. The expression of EGFR on sebocytes seems to play a role in the localization of the rash (18). The body areas most often affected by comedonal and papulopustular lesions are rich in sebaceous glands, although the rash is histologically different from that present in acne vulgaris (8,19). In our patients, the head and upper torso were most frequently involved, which is consistent with the literature data concerning mAbs directed against EGFR (20). The rash in our

**Table 3.** Literature data about skin-related cetuximab adverse effects (3,11-15)

| | | Saltz *et al.* 2004 (11) | Lenz *et al.* 2006 (12) | Jonker *et al.* 2007 (3) | Tol *et al.* 2008 (15) | Raoul *et al.* 2009 (13) | Rodriguez-Murphy *et al.* 2010 (14) |
|---|---|---|---|---|---|---|---|
| Any rash | | 86 | 82.9 | 88.6 | 92 | 52 | 69.8 |
| Grade 1 | | no data | no data | 39.6 | 55 (G1+G2) | no data | 48.3 |
| Grade 2 | | no data | no data | 37.2 | | no data | 44.8 |
| Grade 3 | % of patients | 18 | 4.9 | 11.8 | 26 (G3+G4) | 12 | 10.3 |
| Grade 4 | | no data | no data | 0 | | no data | 0 |
| Allergic reaction (G3) | | 5 | 7.5 | 2.8 | 7 | no data | 6.9 |
| Periungueal lesions | | 12 | 16.5 | no data | 32 | no data | 7 |
| Hipertrichosis | | no data | no data | no data | no data | no data | 4.7 |

**Figure 5.** Hipertrichosis.

patients was usually mild to moderate (G1 in 27%, G2 in 51.4%), which is consistent with the results published in the above-mentioned studies (3,11-15). Severe skin toxicity in Grade 3 occurred less commonly; however, in one of our patients, treatment was terminated due to lesions on the top of the fingers, and four patients had administration of cetuximab temporarily discontinued because of its toxicity.

Canadian Treatment Recommendations advise topical clindamycin and steroids as a treatment for mild and severe skin rash. These agents reduce inflammation which has been connected with EGFR inhibition (21). The occurrence of moderate or severe skin toxicity may demand the use of oral tetracycline antibiotics. These agents are characterized by matrix metalloproteinase inhibition which results in anti-inflammatory properties. When duration of skin lesions is longer than 1-2 weeks despite treatment, or if other severe symptoms, such as necrosis or petechial or purpural lesions occur, referral to a dermatologist is advised (10).

Other recommendations for therapy with mAbs in the Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) , are based on topical corticosteroid hydrocortisone 1% and semisynthetic tetracycline analog doxycycline a moisturizer and sunscreen used in prevention of skin toxicities starting from the 1st to 6th week of the therapy with mAb (22). This treatment, also used for the side effects of cetuximab, is a result of four main alterations caused by mAbs directed against EGFR: skin inflammation, bacterial superinfection, dry skin, and skin sensitivity to ultraviolet radiation (22).

Patients treated with cetuximab can develop dry, scaly, itchy skin, located especially at the earlier localization of the acneiform eruption (23). Excessive dryness of the skin can cause eczema and painful,

bleeding fissures (19). Fissures which develop on the fingertips and toes make it difficult to perform daily activities. Abnormal skin dryness caused by cetuximab can be explained by the role of EGFR in reduction of the epidermis permeability (24). For primary prophilaxis of these changes, patients should be informed about the necessity of sun protection and of avoiding activities and products which could dry their skin (10). Emollients should be used in treating fissured skin (25).

In our study, periungueal changes were observed in 20% of the patients – more often than in the literature where paronychia, painful inflammation of a fingernail or toenail fold, occurs in 10% to 15% of patients treated with cetuximab (16,26) (Figure 3). Severe lesions of fingertips and paronychia resulted in discontinuation of therapy in one case. Antiseptics, oral or topical antibiotics and, in severe cases, steroids are helpful in the treatment of paronychia. The route of administration of antibiotics depends on the severity of lesion (9,26).

Hair changes can be also observed during cetuximab therapy. Significant trichomegaly is an example (not graded according to CTCAE v. 4.0). It manifests in long and rigid, sometimes curly lashes (Figure 4). It appeared in five cases during our study. This is a typical side effect of EGFR inhibitor therapy (27). Trichomegaly in combination with xerophthalmia can cause bilateral ocular discomfort, foreign body sensation and tearing. In some cases, it may impair vision. If the eyelashes become too long and start to irritate the surface of the eye, they should be cut (28). Another side effect concerning hair – hypertrichosis – was noticed in one of our patients treated with cetuximab (Figure 5). Alopecia was also observed among our patients. However, due to insufficient data in patient records, it was impossible to estimate the frequency and severity of alopecia in our population. Loss of hair can occur on the scalp and extremities, whereas hypertrichosis appears on the back, on female lips, and on the face (16). These changes suggest that the mechanism regulating hair growth may vary in different parts of the body.

Serious allergic reactions are observed in 2.8-7.5% of patients according to the literature data (3,11-15), which is in agreement with the results of our study (7%). In three of our patients, severe infusion reactions from cetuximab appeared after the first dose. Severe infusion reactions are a contraindication for the continuation of cetuximab therapy (29).

Analysis by Jatoi *et al.* shows correlation between the sex and age of patients and the severity of the rash during cetuximab therapy. In their study, more

men than women developed rash in Grade 3: 34 (7%) versus 16 (3%) (multivariate odds ratio 2.12; $P$=0.017). Grade 3 rash also occurred in younger patients (<70 years of age): 48 (6%) versus 2 (1%) (multivariate odds ratio 0.21; $P$=0.032). In contrast to the literature, in our group older patients were at greater risk of rash in Grade 3: 2 (5.4%) after 55 years of age versus 1 (2.7%) before 55 years of age. All Grade 3 rashes developed in men: 3 (8.1%), all women suffered from rash in G1 or G2. It should be noted that our results are not predictive (odds ratio for age and gender $P$=0.3086 and $P$=0.7689, respectively). It is likely that the absence of a statistically significant association between the presence of rash and age or gender was caused by the small number of patients in the study. It is possible that correlation exists and may be observed in larger groups of patients.

This study has some limitations as a result of its retrospective nature and the group size. Patient data and their treatment histories were gathered from medical records. Occasionally, information about adverse effects was incomplete (e.g. lack of information about the severity of the symptom). When any concern about the patient history occurred, it was discussed with the oncologist treating the patient. It is important to note that in order to provide sufficient and timely dermatological treatment for such patients, the oncologists should be more attentive in description of side effects. Moreover, adverse effects which occur rarely should be described in detail. The statistical analysis that was performed is not predictive on grounds of the wide variety and small number of patients in the study.

This study shows that cetuximab-related adverse effects present their specific features regardless of the concomitant chemotherapy. Knowing the main symptoms of possible adverse effect allows the safety of the therapy to be monitored and early treatment of skin lesions, before they cause the treatment to be discontinued.

## CONCLUSION

Therapy with mAbs is characterized by a specific profile of adverse effects which affect the skin and appendages especially. These side effects are usually not life-threatening, but if severe can require cessation or temporary termination of therapy. Moreover, skin lesions can bring on social or emotional anxiety. Therefore, it is important to prevent such skin toxicities through proper care and early cooperation between the oncologist and dermatologist.

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