

Acne during adolescence did not predict skin rash reaction to cetuximab

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Cetuximab, a monoclonal antibody, is a part of the treatment for metastatic colorectal cancer. The most common side effect of cetuximab is skin rash, which has a similar distribution to acne vulgaris and some overlapping pathophysiological mechanisms. The aim of the current study was to determine whether acne vulgaris in adolescence (AinA) is predictive of a cetuximab-related rash to better understand the pathogenesis of this side effect and explore potential preventive actions. From July 2013 to June 2015, patients with metastatic colorectal cancer planned for treatment with cetuximab were enrolled in the study. Before initiating treatment, patients completed a questionnaire evaluating endocrine disorders, other chronic diseases, smoking, chronic medications, allergies, and dermatologic history of AinA and its severity. Patients were followed for 6 months. Data were collected from 32 participants (16 women, 16 men). Twenty-three (69%) patients experienced a cetuximab-associated skin reaction. Nine (28%) patients had a history of AinA. Of these, seven developed a cetuximab-associated skin reaction. Three of the five (60%) patients who used proton pump inhibitors (PPIs) developed severe (grades 3–4) skin toxicity versus 4/27 (15%) patients who were not on PPIs ($P=0.057$). The

degree of skin toxicity correlated to the median time-to-tumor-progression: 2 months for patients with grades 0–1 compared with 5.5 months for grades 2–4 skin toxicity ($P=0.047$, 95% confidence interval 1.06–4.95). No significant correlation was found between AinA and cetuximab-associated skin reactions. The correlation between PPI treatment and severe skin toxicity related to cetuximab should be examined further. *Anti-Cancer Drugs* 00:000–000 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Cetuximab is a chimeric IgG1 monoclonal antibody that binds the epidermal growth factor receptor (EGFR). It is approved for patients who have metastatic colorectal cancer (mCRC) expressing wild-type RAS, a signaling protein in the EGFR pathway, or for patients with squamous cell cancer of the head and neck. EGFR is a transmembrane glycoprotein that belongs to the HER-family of tyrosine kinases. The main ligands for this receptor are epidermal growth factor (EGF), transforming growth factor alpha, amphiregulin, and betacellulin. Induction of the receptors by EGF induces DNA replication, repair, and cell growth through a tyrosine kinase pathway. EGFR also promotes and regulates angiogenic factors. Inhibition of those receptors with cetuximab inhibits cell growth, induces apoptosis, and decreases the production of various DNA repair proteins. In addition, cetuximab signals for EGFR internalization and degradation [1,2].

Adding cetuximab to first-line chemotherapy in patients with RAS wild-mCRC significantly improved treatment

outcome compared with chemotherapy alone, with a median survival greater than 24 months [3,4]. The combination of chemotherapy and cetuximab was also found to improve survival, time-to-tumor-progression (TTP), and response rate after progression of previous chemotherapy combinations [5,6].

The most common side effect of cetuximab, occurring in over 80% of patients, is an acneiform eruption, with grade 3 or 4 toxicity, in over 25% of patients [7]. This acneiform rash presents in sebaceous areas of the scalp, face, and upper trunk, with clusters of monomorphic pustular lesions, usually localized to the hair follicles on sun-exposed areas. The rash is related to the high levels of EGFR in the sebaceous glands. Inhibition of EGFR signaling in the skin causes abnormalities in basal keratinocyte maturation, growth, and migration [8]. Studies of cetuximab have shown that patients with a higher-grade acneiform rash have increased response rate, TTP, and overall survival [9]. For this reason, a severe skin rash is not an absolute contraindication to cetuximab. Grade 2 rashes and higher are associated with a decrease in

quality of life, low treatment compliance, and, in some cases, withdrawal from treatment [2]. Only a few studies have examined the predictive factors for an acneiform rash because of cetuximab. A large study of over 900 patients showed that men younger than 70 years of age were more likely to develop a higher-grade rash [10].

A relationship between acne in adolescence and an acneiform rash has been proposed because of the similarity in appearance of the rash as well as the theoretical relationship between acne, androgens, and EGFR [11–14]. This link has only been discussed in the context of prostate cancer and the potential of treating androgen-independent prostate cancer with cetuximab. It has been proposed that EGF downregulates androgen receptors (ARs). Therefore, inhibiting the EGFR response may, in turn, increase ARs. Patients who have a history of hormonally related acne may be more likely to have higher levels of androgens and/or ARs and may show a more exaggerated response to EGFR inhibition with cetuximab, together with a severe rash [11–14].

The aim of this study was to determine whether acne vulgaris in adolescence is predictive of a rash toxicity to treatment with cetuximab in mCRC patients.

Patients and methods

The study protocol and informed consent were approved by our institutional (Helsinki) ethics committee. Patients were enrolled according to the following inclusion criteria: confirmed mCRC, cetuximab treatment as a single agent or in combination with chemotherapy, age older than 18 years, and life expectancy of more than 12 weeks. Patients were excluded if they had previously received any systemic immunotherapy or target therapy for cancer or any other disease (except bevacizumab), presence of previous acne or acneiform rash, or treatment plan of cetuximab and capecitabine.

Before initiating treatment with cetuximab, a questionnaire was administered to the patients, evaluating endocrine disorders, other chronic diseases, smoking, chronic medications, allergies, dermatologic history in terms of a history of acne during adolescence and the severity, demographics, malignancy status, and oncology treatment.

Treatment with cetuximab was administered once a week at a dose of 250 mg/m² body surface area, as a single agent or together with irinotecan, or in combination with 5-fluorouracil and oxaliplatin or irinotecan, every 2 weeks at a dose of 500 mg/m².

Patients were observed for 6 months. During the first 3 months, visits were held every 3–4 weeks. After the first 3 months, the frequency of visits was reduced to every 6–8 weeks. During follow-up meetings, the oncologist used the Common Toxicity Criteria of Adverse Events [15] to evaluate patients who developed a skin reaction and recorded the onset, distribution, severity, and changes in medication.

Patients were then referred to a dermatologist, who further evaluated the rash using a Dermatology Life Quality Index score [16] and prescribed a corresponding treatment protocol.

Statistical analysis

The determination of the sample size for this study was based according to the statistical model that 101 patients were needed to confirm the hypothesis that AinA is predictive for skin side effects of cetuximab and only 32 patients are needed to accept the null hypothesis. Results are presented as descriptive statistics. Predictive variables were tested using the χ^2 and *t*-tests. A logistic regression model was used to calculate the odds ratio. Interim analysis was planned after 32 patients to reject or accept the null hypothesis.

Results

This study included 32 patients with mCRC, 16 men and 16 women. The average age was 62 years (range, 34–84 years). Patients' clinical characteristics are summarized in Table 1. Nine (28%) patients had a history of AinA, with an average initial appearance of rash at age 14.5 years and an average resolution age of 17.9 years. The history of AinA is summarized in Table 2.

Cetuximab skin toxicity

Twenty-two of the 32 (69%) patients experienced a rash with cetuximab: 12/16 (75%) women and 10/16 (62.5%) men. Cetuximab rash appeared on an average of 16 days and SD $\pm$ 15 days (range, 3–56 days) from the initiation of treatment. Rash appeared on an average of 15.5 days (SD: 15.5 days) in patients without AinA and 18.6 days (SD: 15.1 days) in patients with AinA. Of the 12 women who showed skin toxicity, five had grades 3–4 rash and of the 10 men, two had grade 3 rash and none had grade 4 rash. Of the women who developed grade 4 cetuximab rash, one had a history of severe acne and one did not. Ten patients had a cetuximab rash restricted to the face and

Table 1 Patients and treatment characteristics

Characteristics	Number of patients
Men/women	16/16
Age: < 70/ > 70 years	21/11
BMI: < 25/25–29/ > 30	11/15/6
Metastatic site	
Liver	20
Lungs	7
Abdominal and pelvic lymph nodes	11
Peritoneum	5
Other organs	13
Patients with previous treatments	27
Patients with previous bevacizumab combinations	18
Cetuximab first line	5
Cetuximab second line	17
Cetuximab third line	9
Cetuximab-5FU-based combination	26
Cetuximab, irinotecan	6

5FU, 5-fluorouracil.

Table 2 Demographics of patients with acne in adolescence

Average age acne appeared	14.5 (range, 12–16 years)
Average age acne resolved	17.9 (range, 13–25 years)
Distribution of acne rash	All over face
Severity of acne in adolescence	
Grade 1	5M/2F
Grade 2	1F
Grade 3	1F
Family history of acne	4
Who was responsible for treatment	
Self	6
Physician	1
Physician and cosmetician	1
Type of treatment	
Topical antibiotics	2
Oral and topical antibiotics	1
Scars after recovery	3/9
Female patients with menstrual disturbances	2/4

F, female; M, male.

the rest of the patients had a rash distribution that extended beyond the face. Of the patients with AinA, seven (78%) developed cetuximab-related rash compared with 15/23 (65%) of the patients without a history of AinA. Data are shown in Table 3.

Predictive factors for cetuximab-induced skin toxicity

The χ^2 -test was performed to determine whether cetuximab skin reaction was related to age, sex, severity of acne in adolescence, and proton pump inhibitors (PPIs) use as the most common drug used by the patients with grade 3 toxicity. A comparison was made for grades 0–2 versus grades 3–4. The *P* value was found to be insignificant in all associations (Table 4). Interestingly, a near-

Table 3 Cetuximab skin toxicity

	Total	Acne in adolescence (total 9 patients)	No history of acne (total 23 patients)
Severity (grade) of cetuximab skin toxicity			
0		2 (1M/1F)	8 (5M/3F)
1		3 (1M/2F)	6 (3M/3F)
2		3 (3M)	3 (1M/2F)
3		0	5 (2M/3F)
4		1 (1F)	1 (1F)
Severity of skin toxicity < 70 (21 patients)			
0	6	1	5
1	5	3	2
2	5	3	2
3	3	0	3
4	2	1	1
Severity of skin toxicity > 70 (11 patients)			
0	4	1	3
1	4	0	4
2	1	0	1
3	2	0	2
4	0	0	0
Distribution of rash			
Face		1	9
Face and chest		0	2
Face, upper back, chest		3	2
Face, upper and lower back, chest		1	
Patients who needed chemoreduction		2	9

F, female; M, male.

Table 4 Predictive factors for cetuximab skin toxicity

	Grades 0–2	Grades 3+	<i>P</i> value
Age (years)			0.669
< 60	10	4	
> 60	15	3	
Sex			0.394
Male	14	2	
Female	11	5	
Severity of acne in adolescence			0.109
Grade 0	17	6	
Grade 1	7	0	
Grade 2	1	0	
Grade 3	0	1	
PPI use			0.057
Yes	2	3	
No	23	4	

F, female; M, male; PPI, proton pump inhibitor.

significant correlation was found for PPIs and cetuximab skin toxicity. Five (16%) patients reported taking a PPI. Of the seven patients who developed a grade 3+ reaction, three were on PPIs (3/5 patients, 60%) and four were not on PPIs (4/27 patients, 14.8%). This comparison was close to statistical significance, with *P* = 0.057.

The median survival time was 15.3 months (range, 4.2–26.3 months). The average TTP from the start of cetuximab was 5.77 months (range, 0.5–18.5 months). The median TTP was 2 months for patients with grades 0–1 and 5.5 months for grades 2–4 rash (*P* = 0.047, 95% confidence interval 1.06–4.95). Overall survival was not correlated with the severity of rash (*P* = 0.72).

Discussion

Cetuximab-associated skin toxicity can influence a patient's quality of life, leading to depression, anxiety, and social withdrawal, ultimately leading to disruptions in treatment plan [17,18]. Predicting a severe skin toxicity to cetuximab may help in understanding the pathophysiology of the rash and also in attempts to develop preventive measures and enhance patient's compliance. Currently, there are no predictive factors for cetuximab-induced severe skin toxicity. The only clue came from a prospective study that included over 900 mCRC patients, suggesting that men compared with women and age younger than 70 years are risk factors for a severe (grade 3) cetuximab-induced rash, even though the absolute risk of severe rash was low (<10%) [10]. This finding may be supported by the finding from immunohistochemistry that the expression of EGFR decreases with age [19].

Sex differences have been discussed within the context of acne and wound healing as hormonal differences can affect pore size, sebum production, immune response, and skin thickness and elasticity [20,21]. In the present study, more female patients younger than 70 years of age had a grades 3–4 rash (5/12) versus no women 70 years of age and older (0/4). This finding is consistent with previous studies that have shown that younger patients are more likely to develop a cetuximab-induced skin rash.

Because of the small cohort of patients who developed severe rash, it is impossible to draw any conclusions from the present results.

It was proposed that AinA may be associated with a more severe rash from cetuximab because of similarities in the appearance of the rash and the relationship and crosstalk between ARs and EGFR [11–14]. Both EGFR and AR are found in sebaceous glands [8,22]. The AR is a nuclear receptor found in the cytoplasm of the cell and, when activated by androgenic hormones, the receptor can translocate to the nucleus and activate gene transcription [23]. In prostate cancer cell lines, the AR typically found in the nucleus can translocate and attach to EGFR found on the cell membrane, effectively inhibiting EGFR signaling and leading to decreased invasion and malignancy in prostate cancer. With this translocation, cell lines show an increased sensitivity to androgens and, in turn, increased AR activation. Thus, EGFR inhibition is inversely correlated with increased AR activity and a reversal of androgen-independent prostate cancer to androgen-sensitive prostate cancer [24].

Patients with acne tend to have increased levels of androgens, even though there is no positive correlation between the severity of acne and hormone levels [25,26]. In addition, androgens and AR have been shown to enhance inflammatory responses of macrophages and neutrophils, which may worsen the inflammatory response to cetuximab [27,28]. Although the predictive value of acne in adolescence was not found to be statistically significant in the present study, the relationship between ARs and EGFRs should be investigated further.

In this study, the most relevant and surprising finding was that 3/5 (60%) patients who used PPIs developed severe skin toxicity compared with 4/23 patients (17%) ($P=0.057$) who did not. Although rare, omeprazole has been associated with a skin rash in 0.5% of patients, including exfoliative dermatitis, disseminated epidermal necrolysis, lichen spinulosus, urticaria, and angioedema [29–32]. Most reports on skin reactions were case studies. A prospective study is planned to determine whether there is any correlation between grade of cetuximab skin reaction and PPI.

The main aim of this study was to determine whether there is a correlation between acne during adolescence and the development of skin rash to determine a predictive factor in developing skin toxicity with cetuximab. This study represents an interim analysis of 32 patients, in which no significant correlation between AinA and skin toxicity because of cetuximab was found.

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Conflicts of interest

There are no conflicts of interest.

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