



Analysis of sebum lipid composition and the development of acneiform rash before and after administration of EGFR inhibitor

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ABSTRACT

Treatment with an epidermal growth factor receptor inhibitor (EGFRI) in patients having non-small-cell lung cancer can cause frequent and diverse skin toxicities, an acneiform rash being one of the commonest. Although the exact pathophysiology of this rash and its development mechanisms remain unknown, investigators have noted that EGFRI-induced skin toxicity might be partly associated with sebaceous gland function. Sebum is composed mainly of the lipids squalene (SQ), wax ester (WE), triglyceride, free fatty acid, and cholesterol, which are secreted mostly from the sebaceous glands and by keratinocytes. We therefore investigated the lipid composition of sebum before and after administration of EGFRI and whether sebum composition was associated with the development of acneiform rash. To investigate any associated changes in sebum gland activity, we focused especially on alterations in the amounts of SQ and WE, which are secreted solely from the sebaceous glands.

In contrast to our expectations, we observed no substantial changes in the lipid composition of sebum before and after administration of EGFRI. Composition varies with the individual; however, the proportion of SQ and WE derived from the sebaceous glands was significantly lower in regions that did not develop acneiform rash than in regions that did. Our results suggest that development of an acneiform rash after administration of EGFRI could be related to sebaceous gland activity. Measurement of the lipid composition of sebum before therapy with EGFRI might predict which patients will be prone to acneiform rash.

KEY WORDS

Skin toxicity, EGFR inhibitor, sebum, sebaceous glands, lipids, skin

1. INTRODUCTION

Epidermal growth factor receptor inhibitor (EGFRI) is increasingly being used in the treatment of non-small-cell lung cancer¹. Administration of EGFRI often results in skin toxicity, and some reports indicate that such toxicity could be associated with a therapeutic response. However, adverse cutaneous drug reactions from EGFRI can lead to discontinuation of therapy, with attendant loss of benefit²⁻⁴.

Acneiform rash, a typical skin toxicity, is a relatively early-onset side effect, usually occurring after 1 week of treatment and reaching maximum intensity after 2-3 weeks. The rash is characterized by erythematous inter- and intrafollicular papulopustules, which are sometimes itchy and painful, and which can lead to physical and psychosocial discomfort. Little is known about the mechanism by which this skin toxicity develops. Investigators have noted that EGFRI-induced skin toxicity might be associated with the sebaceous glands, where epidermal growth factor receptor (EGFR) is expressed⁵. Meanwhile, no publications have looked into the development of skin toxicity with respect to skin physiology, such as sebum lipid profile. Sebum is composed mainly of the lipids squalene (SQ), wax ester (WE), triglyceride, free fatty acid, and cholesterol, which are secreted by the sebaceous glands and through the intercellular lipid bilayer⁶. Secretion of SQ and WE comes mostly from the sebaceous glands, which suggests that the proportions of those lipids to sebum lipids overall might serve as an indicator of sebaceous gland activity. In the present report, we investigated the association between the lipid composition of sebum and acneiform rash before and after administration of EGFRI.

2. METHODS

After obtaining approval from the Kyushu University Hospital ethics committee and written consent

from the subjects, we studied 6 patients (2 men, 4 women; mean age: 70.8 years) diagnosed with non-small-cell lung cancer who were candidates for gefitinib or erlotinib treatment. No patient had a prior history of acne. Two patients were taking a daily antihypertensive drug; no patient was taking any other relevant medication.

Sebum-absorbing sheets were used to collect sebum samples from the face and chest of patients before, and 2 and 6 weeks after, administration of EGFRi. Samples were collected during the day in an air-conditioned examination room at Kyushu University Hospital under normal ambient conditions. Room temperature was 24°C–28°C, and humidity was 25%–58%. High-performance liquid chromatography was used to determine the amount of each sebum lipid (SQ, WE, triglyceride, cholesterol, free fatty acid) in the samples. At the time of sampling, the presence or absence of acneiform lesions on the face and chest was noted.

3. RESULTS

3.1 Sebum Lipids Before and After Administration of EGFRi

The lipid composition of sebum showed no substantial change after administration of EGFRi (Figure 1); specifically, we observed no change in the proportion of SQ and WE to total sebum lipids after EGFRi administration.

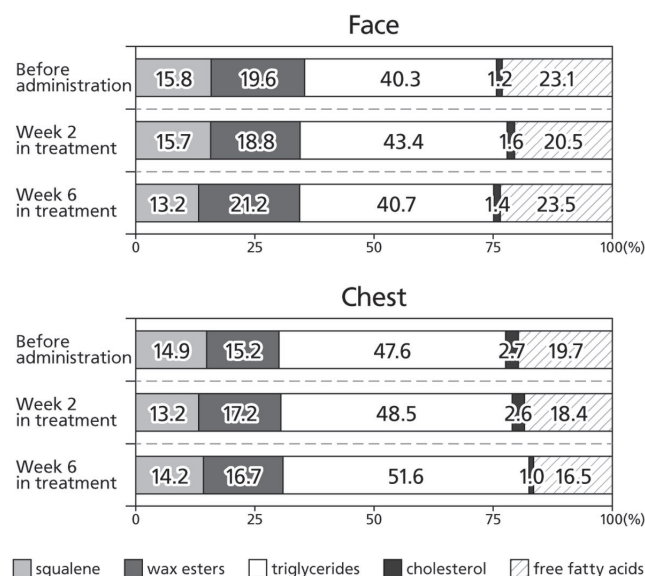


FIGURE 1 Alterations in the lipid composition of sebum in all patients during therapy with epidermal growth factor receptor inhibitor (EGFRi). Before administration of EGFRi, and at 2 weeks and 6 weeks after administration, sebum-absorbing sheets were used to collect sebum from the face and chest of treated patients. High-performance liquid chromatography was then used to determine the proportion of each lipid in the sebum.

Because the intensity of skin toxicity varies with the individual patient, we also performed inter-patient comparisons of the lipid composition of sebum before EGFRi administration. We observed remarkable inter-patient variability in the proportion of SQ and WE, the lipids of sebaceous gland origin (Figure 2).

3.2 Proportion of SQ and WE and Development of Acneiform Rash

Because the inter-patient comparison revealed such variability in lipid proportions, we also investigated possible associations between the ratio of SQ plus WE to total sebum lipids and the development of acneiform rash after initiation of treatment with EGFRi by anatomic region in each patient at each time point. A low ratio was significantly associated with regions in which acneiform rash did not appear during the study (Wilcoxon signed-rank $p < 0.01$, Table 1, Figure 3).

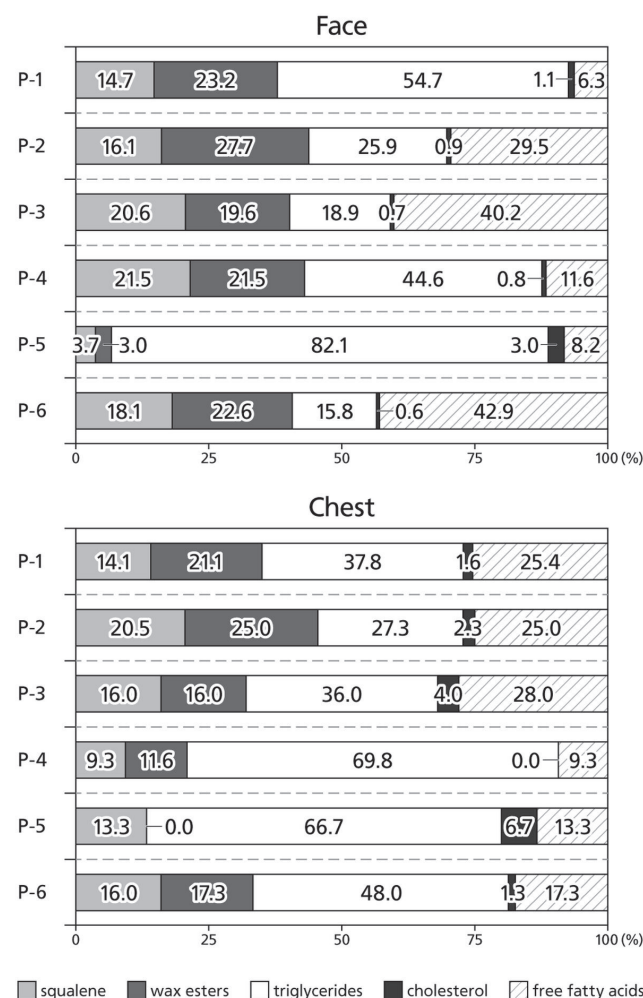


FIGURE 2 Lipid composition of sebum in each study patient before administration of epidermal growth factor receptor inhibitor.

TABLE 1 Association of the ratio of squalene (SQ) plus wax ester (WE) to total sebum lipids (TSL) in patients treated with epidermal growth factor receptor inhibitor, by presence of rash, body region, and time point

Patient		Rash characteristics		SQ+WE:TSL ratio		p Value
Group	ID	Site	Time point (weeks) ^a	Value	Mean	
With rash	P-01	Face	2	41.3	38.1±10.3	<0.01 by Wilcoxon signed rank test
			6	40.8		
	P-02	Chest	2	37.9		
			6	41.4		
	P-03	Face	6	44.9		
	P-04	Face	2	39.4		
			6	33.3		
	P-05	Face	6	7.1		
	P-06	Face	2	42.0		
			6	45.6		
2			39.0			
6			44.7			
Without rash	P-01	Chest	6	38.3	24.2±11.1	
			2	14.2		
	P-02	Chest	6	29.6		
	P-03	Chest	2	32.3		
			6	30.8		
	P-04	Chest	2	8.7		
			6	28.6		
	P-05	Face	2	11.1		
			6	11.1		

^a Sebum lipid measurements are missing at 2 weeks for patient P-03 with rash (because of the patient's physical condition) and at 6 weeks for patient P-02 with rash (because of failure to visit the hospital).

4. DISCUSSION AND CONCLUSIONS

Epidermal growth factor inhibitor seems to predispose to cutaneous toxicity by affecting the sebaceous glands and causing hair follicle inflammation and dyskeratosis⁷. Sebaceous gland dysfunction appears to contribute most to the eruptions, because the acneiform rash develops in the early phase of EGFR treatment^{5,7}. Recently, a study in a mouse model demonstrated increased secretion of sebum from the sebaceous glands because of constant EGFR activation^{8,9}. Further nonclinical studies confirmed that activation of EGFR induces sebaceous gland enlargement and sebocyte proliferation by upregulating the transcription c-Myc^{10–12}, indicating a pivotal role for EGFR signalling in maintaining the size, cell number, and sebum activity of sebaceous glands. The foregoing work indicates a close correlation between sebum activity and EGFR signalling.

The present research shows that regions with low SQ and WE of sebaceous gland origin could have a lower frequency of acneiform rash, which in turn supports the possibility that high sebaceous gland activity could predispose patients to acneiform rash. Thus, our results suggest that pre-treatment

analyses of the lipid composition of sebum could potentially provide a means to predict which patients will be highly predisposed to acneiform rash. In such patients, medications effective in reducing sebum activity—including retinoic acid (tretinoin) and adapalene—might be beneficial, in addition to anti-inflammatory drugs such as steroids and antibiotics, for preventing and treating acneiform rash. The possible association between the development of skin toxicity and the patient's therapeutic response could warrant further analyses with additional patients, but our investigation points to the predictability of acneiform rash development based on a measurement of sebum lipid composition (and, potentially, the predictability of clinical benefit from EGFR).

The conclusions in this report are based on research involving a limited number of patients and skin regions, and thus further investigations with additional skin regions in a larger patient population are warranted.

5. ACKNOWLEDGMENTS

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FIGURE 3 Typical acneiform rash of face and chest in this study.

6. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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