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Original Article

Survey on symptomatic cutaneous manifestations of Epidermal Growth Factor Receptor Inhibitors (EGFRI) in oncology patients at a regional hospital

在一家地區性醫院的腫瘤患者在接受表皮生長因子受體抑制劑（EGFRI）後的皮膚表現症狀調查

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Epidermal Growth Factor Receptor Inhibitors (EGFRI) is a new group of target therapy for a number of carcinomas. Its use may result in cutaneous manifestations which indicate a better tumour response to that therapy. We conducted a survey on the cutaneous manifestations in symptomatic oncology patients who were on EGFRI. A total of 34 patients were recruited within the 1 year study period. Papulopustular eruption (20.5%) was the most common skin manifestation, followed by pruritus (19.9%) and dry skin (19.2%). The relatively low incidence can be explained by the study design which only symptomatic patients were recruited. Five patients (14.7%) had their treatment withheld due to intolerable cutaneous side effects. Collaboration between clinical oncologist and dermatologist should minimize the cutaneous side effects and enhance the compliance of these patients to this life-prolonging therapy.

表皮生長因子受體抑制劑是用於多種癌症的新類型標靶治療。使用這種治療可能引致各種皮膚副作用，但這也反映該腫瘤對治療有更好的反應。我們進行了一項調查，對於用上了表皮生長因子受體抑制劑而有皮膚症狀的腫瘤患者進行評估。在一年的研究期間，共招募了34名患者。丘疹膿庖疹（20.5%）是最常見的皮膚症狀，其次爲瘙癢（19.9%）和皮膚乾燥（19.2%）。這調查中的發病率相對較低，是因爲這研究只招募了有癥狀的患者。五位病人（14.7%）由於無法忍受皮膚的副作用，他們曾被暫停治療。臨床腫瘤科醫生和皮膚科醫生之間的合作可盡量減少皮膚的副作用，從而提高患者可持續地使用這種可延長生命的治療。

Keywords: Cutaneous manifestations, EGFRI, Epidermal Growth Factor Receptor Inhibitor

關鍵詞：皮膚表現，EGFRI，表皮生長因子受體抑制劑

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Introduction

Epidermal Growth Factor Receptors (EGFR) is a family of transmembrane receptor involved in cell proliferation and survival signals,[1] they are important in tumourigenesis as evidenced by their dysregulation occurring in different types of tumours.[2,3] By targeting these receptors, anti-cancer therapy is expected to have less systemic side effects than conventional therapy. However, EGFR is also found in normal keratinocytes, sebaceous and eccrine epithelium.[4,5] These targeted therapies in turn may give rise to various cutaneous side effects so severe that the therapy dose may have to be reduced or even terminated.[6]

With the exciting discovery of such new targeted therapy for oncology patients, dermatologists also have to face the emergence of new drug related cutaneous side effects.[7] It is known that with the development of the cutaneous side effects of this new type of drugs, the tumour response and overall survival are better.[8,9]

In this study, we looked at the symptomatic patients who were put on Epidermal Growth Factor Receptor Inhibitors (EGFRI), patients' particulars, together with the symptoms and Dermatology Life Quality Index (DLQI) were recorded.[10] While more oncological patients are receiving the targeted therapy, we should acquire more understanding of the situation locally.

Methods

All patients who were taking EGFRI with symptomatic cutaneous side effects within the one year study period were referred for dermatologist assessment. The type of cutaneous manifestation and disease grading were assessed by a single observer dermatologist, Dr. Yeung KH. Chinese version of DLQI questionnaire was given to patient to fill-in, and the results were recorded and analysed.

Results

During the study period between May 2010 and May 2011, a total of 156 patients had been commenced with EGFRI. Among these patients, 34 patients (21.8%) were referred to the study by oncologists and being assessed by a single dermatologist (Table 1). The patients were all Chinese, with 14 males and 20 females, the average age was 58, ranged from 42 to 87. A large proportion of our subjects (28, 82.4%) suffered from carcinoma of lung, followed by colorectal carcinoma (4, 11.8%), one with hepatocellular carcinoma and one with carcinoma of breast.

Most of our patients received a tyrosine kinase inhibitor: Erlotinib (17, 50%), followed by Gefitinib (11, 32.4%). Sorafenib, Imatinib and Lapatinib were less used in the study. The monoclonal antibody group, namely Cetuximab, was used in two patients (2, 5.9%), and both suffered from colorectal carcinoma.

Nearly all of our patients did not have any previous history of skin problems before the commencement of EGFRI. Two patients had history of a non-specific itchy skin rash, and one had a history of solar elastosis.

The effect of cutaneous manifestations on quality of life was assessed by the Chinese version of the DLQI questionnaire. The mean score was 10.2 with range between 1 and 29, standard deviation 5.69.

In our study, the most common cutaneous manifestation was papulopustular eruption (Table 2). Symptomatic papulopustular eruptions occurred in 32 patients (20.5%). Onset of the eruptions ranged from immediate to three months after commencement of EGFRI. Based on the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 scoring system, 15 patients were categorised into grade 1 and 2 respectively while only two patients belonged to grade 3. Sebum-rich areas including face, chest

Table 1. Symptomatic cutaneous manifestations of EGFRIs

		No. of patients	Percentage
Papulopustular eruptions (32/156; 20.5%)			
Area involved (can be more than 1 in 1 patient)	Face	24	37.5%
	Chest	13	20.3%
	Scalp	12	18.8%
	Back	7	10.9%
	Limbs	5	7.8%
	Suprapubic	3	4.7%
Grading	Grade 1	15	46.9%
	Grade 2	15	46.9%
	Grade 3	2	6.2%
Pruritus (31/156; 19.9%)			
Area involved (can be more than 1 in 1 patient)	Generalised	13	37.1%
	Limbs	7	20%
	Face	6	17.1%
	Back	3	8.6%
	Scalp	3	8.6%
	Trunk	2	5.7%
	Suprapubic	1	2.9%
Grading	Grade 1	14	45.2%
	Grade 2	17	54.8%
Dry skin (30/156; 19.2%)			
Area involved (can be more than 1 in 1 patient)	Generalised	26	86.7%
	Lips	2	6.7%
	Face	1	3.3%
	Fingers	1	3.3%
Grading	Grade 1	19	63.3%
	Grade 2	11	36.7%
Hair (23/156, 14.7%)			
Pattern	Decreased	11	47.8%
	Increased	7	30.4%
	Curly	4	17.4%
	Whitening	1	4.3%
Grading	Grade 1	22	95.7%
	Grade 2	1	4.3%
Nail changes (17/156,10.9%)			
Area involved	Paronychia	11	64.7%
	Periungual Granuloma	6	35.3%
Grading	Grade 1	6	35.3%
	Grade 2	11	64.7%
Hyperpigmentation (10/156, 6.4%)			
Area involved (can be more than 1 in 1 patient)	Trunk	3	25%
	Limbs	3	25%
	Face	3	25%
	Generalised	1	8.3%
	Sun exposed	1	8.3%
	Neck	1	8.3%
Grading	Grade 1	10	100%

and scalp were the most commonly affected areas. There were totally five patients (14.7%) had intolerable papulopustular eruptions that resulted in withholding of the target therapies. Both patients with grade 3, on erlotinib or gefitinib, had to stop their targeted therapy temporarily or change to another agent because of skin toxicity; their DLQI score was 10 and 19. Three patients with a grade 2 (3/15, 20%) eruption had to stop their targeted therapy or decrease the dose, their DLQI were 9, two of them were put on gefitinib, one was on cetuximab.

Pruritus occurred in 31 patients (19.9%). It was the second most common cutaneous manifestation in our series. Fourteen patients belonged to grade 1, and 17 patients belonged to grade 2 in the severity grading. Skin dryness ranked third in the skin side effects. It mostly affected the whole body and was recorded in 19.2% of patients.

Twenty-three patients, constituting 14.7% of the study population had symptomatic hair changes. Among them, most had decreased hair (11, 47.8%); seven patients (30.4%) had increased in hair growth, and four patients (17.4%) had curly hair. Whitening of hair occurred in one patient (4.3%). Nail changes 17/156 (10.9%) and hyperpigmentation 10/156 (6.4%) are less commonly reported in our study.

Treatment was given or modified by the attending dermatologist. Topical steroid preparations was given to 27 patients, emollients were given to 16 patients, topical antibiotics were prescribed to 18

Table 2. Comparison of prevalence with other studies

	Our study	Other studies[5]
Papulopustular eruption	20.5%	60-80%
Pruritus	19.9%	8-57%
Dry skin	19.2%	4-35%
Hair changes	14.7%	5-6%
Nail changes	10.9%	6-12%
Hyperpigmentation	6.4%	–

patients, eight patients treated with systemic antibiotics, antihistamine was given to 3 patients, and nail topical applications were given to seven patients. Topical eye drops were given to two patients. Six patients with periungual granuloma required 10% topical silver nitrate application.

Discussion

Cancer cells are difficult to kill as they have several abilities like self-sufficiency in growth signaling, evading apoptosis, and sustained angiogenesis. Conventional chemotherapy usually targets the accelerated tumour cell proliferation which is particularly toxic to cancer cells, but is also damaging to healthy cells especially in the bone marrow,[2] hair and intestinal mucosal cells. These side effects may limit the use of effective doses of chemotherapy.

The new molecular targeted therapies are directed against molecular abnormalities that are implicated in the neoplastic transformation process. The Epidermal Growth Factor Receptor was first described by Nobel Prize winners Stanley Cohen and Rita Levi-Montalcini. These transmembrance receptors with tyrosine kinase enzymatic function are involved in cell proliferation and survival signals.[1,5] Upregulation of these receptors was noticed in a number of solid tumours like lung, colorectal, pancreatic and head & neck carcinomas.[6] This would subsequently lead to uncontrolled cell growth, which predisposes cancer formation. EGFR is expressed in undifferentiated keratinocytes, sebaceous epithelium, eccrine epithelium in normal individuals.[4] Inhibiting EGFR expression by the targeted therapy thus can lead to the various cutaneous manifestations. Despite the known cutaneous manifestations, only 8% of the health providers would consult dermatologists.[6]

Papulopustular eruption, as in other published articles, is also the commonest cutaneous manifestation in our study. It mostly occurred in sebaceous area.[2] Other studies reported its occurrence mostly within two weeks of drug commencement.[11] In the 32 patients who had developed papulopustular eruptions in our study, 22 patients (68.8%) developed the eruptions within two weeks, five patients (15.6%) developed eruptions between two and four weeks, and the remaining five patients (15.6%) developed their eruptions one month after drug commencement.

This study found a lower incidence of skin manifestations compared to other studies: papulopustular eruptions accounted for around 60-80% in other study while we had a much lower prevalence of 20.5%.[5] This may be accountable by the study design as we only recruited symptomatic patients referred by oncologists, therefore patients without or having only mild skin manifestations would not have been assessed in our study. In the survey done in the United States, most of the papulopustular rashes seen by the oncologists are mild in severity.[6]

The effect on patients' quality of life from the above cutaneous manifestations was measured by DLQI. DLQI was calculated by summing the score of 10 validated questions resulting from zero to 30. The higher the score, the more impairment in quality of life there would be. The mean DLQI in our study was 10.2, which translates to moderate effects on patients' life quality.[10]

Our study demonstrated a one year survival rate of 88.2% (30/34). The four patients who passed away within one year all suffered from stage 4 lung carcinoma. The mean age of the four patients (62.3 years) was slightly higher than the mean age of the whole study population. The male to female was 1:1. Among the stage 4 lung carcinoma patients in our study, the one-year survival rate was 80% (16/20). However, as the study case number is small, an improvement in survival for local symptomatic EGFRI patients should be further studied.

Limitations

Due to resource and manpower constraints, we could only screen those patients with symptomatic EGFRI induced cutaneous toxicity, explaining the relatively lower incidence of cutaneous side effects when compared with other studies which screen all patients put on EGFRI. However, this does not affect the clinical significance of our study as we should only treat those symptomatic cases. But it may be difficult to compare our findings with other studies.

In our study, we adopted the DLQI as our measure for the change of life quality in these patients. However, the DLQI is designed for those patients with general skin disorders, which may have different epidemiological characteristics from our patients (e.g. older age group, different expectation for limited life span). In the future studies, a newly designed validated scale should be developed for this kind of patient group.

Last but not least, we could not follow up the progress of each patient. Only those with severe cutaneous toxicities were referred to our dermatology center for further management. This limited our study to a cross sectional observation. It would have been more comprehensive if we can conduct a longitudinal follow up for every patient in our study.

Although the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 scoring system is the most widely used method of grading in EGFRI induced cutaneous toxicities, it puts more emphasis on the impact of daily activities rather than the physical observation of the cutaneous manifestations which our dermatologists usually used. It is designed as a surveillance tool. For example, certain grading criteria basing rash severity on body surface area are misleading because EGFRI-induced papulopustular rashes can be very severe but are generally confined to the face and upper trunk which covers less than 20% of the total body surface area. Without formal training in dermatology, it may be difficult for the oncologist to assess the severity of cutaneous toxicity accurately and objectively. This may lead to inconsistent assessment. Different evaluations between dermatologists and oncologists may lead to inconsistent assessment. Therefore, the liaison between oncologists and dermatologists both in studying and managing these kinds of cutaneous toxicities is very important.

Conclusion

EGFRI are relatively new type of medications; its cutaneous toxicities are common side effects in EGFRI treated patients, and may give rise to significant patient distress thus potentially limiting its use. It was found that as much as one third of the attending oncologists discontinued or lowered the dose of EGFRI due to cutaneous toxicities, thus may interfere with this life-prolonging treatment.[6] Most of these cutaneous toxicities are manageable,[12] and collaboration between the clinical oncologist and dermatologist should be encouraged to minimised the impact of these side effects to the patients' quality of life and enhance the compliance of these patients to the EGFRI.

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