Cutaneous Side Effects of Epidermal Growth Factor Receptor Inhibitors (PRIDE syndrome) in Patients with Non-small Cell Lung Cancer: A Cross-sectional Study from Hatyai Hospital, Southern Thailand

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ABSTRACT:

RONGNGERN P*, NAKWAN N, TANTIVITHIWATE T***, WATCHIRAKAEYOON P***. CUTANEOUS SIDE EFFECTS OF EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS (PRIDE SYNDROME) IN PATIENTS WITH NON-SMALL CELL LUNG CANCER: A CROSS-SECTIONAL STUDY FROM HATYAI HOSPITAL, SOUTHERN THAILAND. THAI J DERMATOL 2021;37:150-60.**

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Received: 30 July 2021 Revised: 2 September 2021 Accepted: 8 November 2021

Background: PRIDE syndrome (Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to Epidermal growth factor receptor inhibitors) is cutaneous adverse events of epidermal growth factor receptor (EGFR) inhibitors. Numerous studies show a correlation between the presence and severity of PRIDE syndrome and tumor response. However, previous studies about cutaneous adverse events are still limited especially in Asian and Thailand.

Objectives: This study aims to investigate the cutaneous adverse events of EGFR inhibitors and to explore correlations between cutaneous adverse events with patient's factors and tumor response.

Methods: A single center, retrospective cross-sectional study, conducted in Hatyai hospital from September 2014 to June 2020. All medical records from 74 patients with stage IV non-small cell lung cancer who received EGFR inhibitors were retrieved and analyzed.

Results: In all 74 patients (53 females ,21 males), 41 (55.4%) patients received afatinib, 20 (27%) patients received gefitinib and 13 (17.6%) patients received erlotinib. Cutaneous adverse events occurred in 47 (63.5%) patients. The most common adverse events were xerosis (65.9%), paronychia (57.4%) and papulopustular rash (42.6%). PRIDE syndrome had statistically significant association with tumor response *(P=0.001).* However, there was no statistically significant association between patient's factors and cutaneous adverse events.

Conclusions: PRIDE syndrome is common in Thais. The most common adverse events were xerosis. We also found statistically significant association between PRIDE syndrome and tumor response, supporting PRIDE syndrome can be used as a marker of tumor's treatment outcome.

Key words: Afatinib, cutaneous adverse events, epidermal growth factor receptor inhibitors, erlotinib, gefitinib, non-small cell lung cancer, PRIDE syndrome

Introduction

The epidermal growth factor receptor (EGFR) inhibitor is targeted therapy. Mechanism of action is to inhibit epidermal growth factor by interfering with the intracellular binding between adenosine triphosphate and tyrosine kinase enzyme through EGFR receptor activation, resulting in intracellular inhibition of tumor cell growth. EGFR inhibitors are first-line therapy for advanced-stage or stage IV non-small cell lung cancer patients with EGFR mutation, including erlotinib, gefitinib, and afatinib.

PRIDE syndrome (Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to epidermal growth factor inhibitors) is cutaneous adverse events of epidermal growth factor receptor inhibitors[1-3]. Previous studies have been reported

that PRIDE syndrome occurred about 50-96.7%[3-10]. Patients' factors related to these adverse events are drug doses[7], age[9] and PRIDE syndrome also related to tumor response[4,6-9,11,12], therefore PRIDE syndrome can be used as a marker of tumor's treatment outcome. However, these adverse events may interfere the treatment compliance, alter drug doses, treatment interruption and worsen patients' quality of life[4,5].

Previous studies about cutaneous adverse events are still limited, especially in Asia and Thailand. So, this study aims to collect data about the prevalence and characteristics of PRIDE syndrome, the factors related to cutaneous adverse events and association between cutaneous adverse events and tumor responses in advanced-stage non-small cell lung cancer patients who treated with epidermal growth factor receptor inhibitors in Hatyai hospital, Songkhla, Thailand.

Methods

A retrospective cross-sectional study was conducted with approval from ethic committee of Hatyai hospital, Songkhla, Thailand (Protocol number 10/2564) Patients with stage IV non-small cell lung cancer who were received EGFR inhibitors at pulmonary unit, department of Medicine and developed cutaneous adverse events were referred to the dermatology clinic. Two dermatologists evaluated the patients and recorded dermatologic findings in the medical record. The medical records of patients treated from 2014 to 2020 were retrospectively reviewed. Demographic characteristics data, subtypes of non-small cell lung cancer, treatment line of EGFR inhibitors, previous chemotherapy treatment, characteristics of cutaneous adverse events, duration from drug initiation to first cutaneous adverse event and and tumor responses were collected and analyzed.

Treatment line defined as, first-line is patients using EGFR inhibitor first after diagnosis of advanced-stage non-small cell lung cancer, second-line is patients using EGFR inhibitors after treated with one standard chemotherapy formula and later-line is using EGFR inhibitor after at least two standard chemotherapy formulas. Tumor response evaluation by the Response Evaluation Criteria In Solid Tumors[13]. In this study, patients who experienced stable disease, partial response, or complete response after EGFR inhibitors treatment were defined as responders. Patients who met with progressive disease criteria were defined as non-responders.

Statistical analysis

Data were analyzed using SPSS (version 26.0; SPSS Inc, Chicago, IL, USA). Categorical variables were summarized as number of frequencies, percentage, while continuous variables were presented in terms of mean ± standard deviation

or median with interquartile ranges. Correlation between cutaneous adverse events and tumor response was determined using the Chi-square test or Fisher's exact test. In univariable analysis, logistic regression models were used to identify factors associated with PRIDE syndrome. A P-value less than 0.05 indicated statistically significance.

Result

Demographic characteristics

Total of 74 patients (53 female, 21 male) received EGFR inhibitors. Demographic characteristics data is shown in Table 1. The mean age was 62 ±11.59 years. Type of lung cancer mostly was adenocarcinoma (90.5%) and squamous cell carcinoma (9.5%). Forty-one patients (55.4%) received afatinib either 30 or 40 mg/day orally. Twenty patients (27%) received gefitinib 250 mg/day orally, and thirteen patients (17.6%) received erlotinib 150 mg/day orally. Treatment lines were divided into first-line treatment 58 patients (78.4%), second-line 5 patients (6.8%) and later-line 11 patients (14.9%). Some patients who did not receive EGFR inhibitors as first-line were treated with previous chemotherapy (21.6%).

Table 1 Demographic characteristics of 74 patients treated with EGFR Inhibitors

Demographic Characteristic	Study Population (N=74)(%)
Female	53 (71.6)
Age (years), mean ± SD	62 ± 11.59
Subtype of Non-small cell lung cancer	
Adenocarcinoma	67 (90.5)
Squamous cell carcinoma	7 (9.5)
Treatment Line of EGFR inhibitor therapy	
First line	58 (78.4)
Second line	5 (6.8)
Later line	11 (14.9)
Type of EGFR inhibitor therapy	
Afatinib	41 (55.4)
Gefitinib	20 (27.0)
Erlotinib	13 (17.6)
Previous treatments before EGFR inhibitors therapy	
Chemotherapy	16 (21.6)

Cutaneous adverse events

Forty-seven of 74 patients (63.5%) developed adverse events from afatinib 26 patients (55.3%), gefitinib 12 patients (25.5%) and erlotinib 9 patients (19.1%). Afatinib caused numerous characteristic dermatologic findings of PRIDE syndrome. Onset of symptoms occurred mostly within 1 to 3 months after drug initiation. Two patients (4.3%) discontinued treatment due to PRIDE syndrome and three patients (6.3%) were prescribed a decreased dose of EGFR inhibitor. (Table 2)

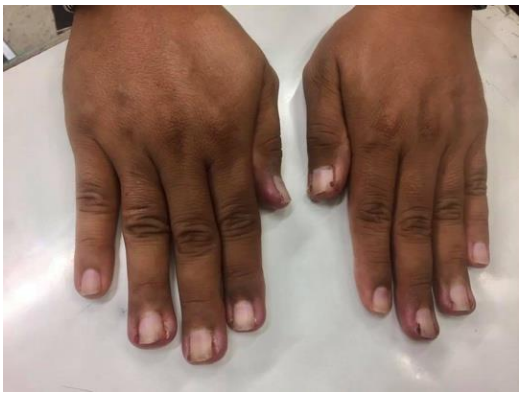

Figure 1 Paronychia. A 60-year-old female with stage IV non-small cell lung cancer developed red and swelling lateral nail fold of all fingers except both little fingers 1 week after gefitinib 250 mg/day

All cutaneous adverse events and onset of symptom after drug initiation were shown in Table 3. The most common adverse events were xerosis (65.9%), paronychia (57.4%) (Figure 1) and papulopustular rash (42.6%) (Figure 2,3). The average onset of xerosis, papulopustular rash, acne, and mucositis was 30 days; pruritus 75 days; paronychia and other nail disorders 60 days; trichomegaly and alopecia 6.5 months.

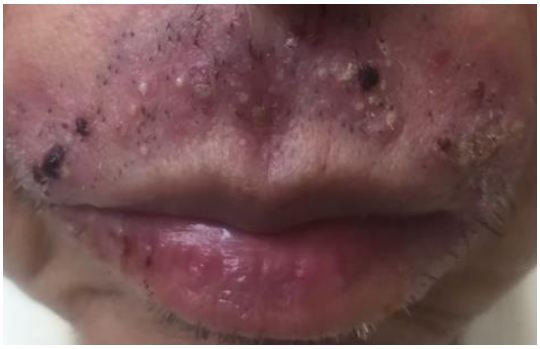

Figure 2 Papulopustular eruption. A 65-year-old male with stage IV non-small cell lung cancer developed papulopustular rash at face and neck 3 weeks after afatinib 40 mg/day

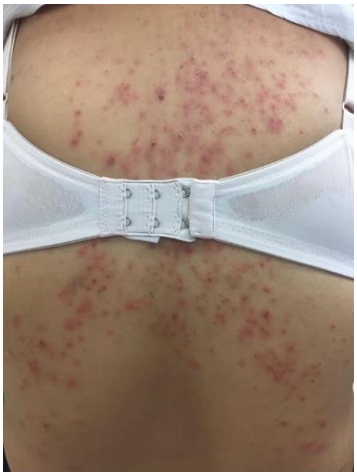

Figure 3 Papulopustular eruption. A 49-year-old female with stage IV non-small cell lung cancer developed papulopustular rash at trunk 1 month after erlotinib 150 mg/day

Risk factors of cutaneous adverse events in patients with stage IV non-small cell lung cancer treated with Epidermal Growth Factor Receptor Inhibitors

Regarding the relationship between demographic characteristics and the occurrence of cutaneous adverse events, there were no significant differences between gender, mean age, subtype of non-small cell lung cancer, treatment-line of EGFR inhibitor, afatinib doses, previous chemotherapy treatment and the cutaneous adverse events *(P>0.05).*

Tumor response

We found a significantly greater tumor response in patients who had PRIDE syndrome compared to those who had no PRIDE syndrome (P = 0.001) (Table 4). No statistically significant difference of tumor response in patients who had two or more different types of cutaneous adverse events compared to those having one (P > 0.05) (Table 5). Regarding the type of cutaneous adverse events and tumor response, papulopustular rash and paronychia were associated with tumor response while other cutaneous adverse events were not (Table 6).

Table 2 Cutaneous adverse events in patients treated with EGFR Inhibitors

Outcome	**Study Population (N=74)(%)**	**Afatinib (N=41)(%)**	**Gefitinib (N=20)(%)**	**Erlotinib (N=13)(%)**
PRIDE cutaneous adverse events	47 (63.5)	26 (55.3)	12 (25.5)	9 (19.1)
Number of **cutaneous adverse event(s) in one patient**				
1	10 (13.5)	5 (50)	3 (30.0)	2 (20)
2	16 (21.6)	8 (50)	5 (31.3)	3 (18.8)
3	11 (14.9)	5 (45.5)	3 (27.3)	3 (27.3)
4	5 (6.8)	4 (80)	0	1 (20)
5	2 (2.7)	1 (50)	1 (50)	0
6	2 (2.7)	2 (100)	0	0
7	1 (1.4)	1 (100)	0	0
Onset of **first cutaneous adverse event** (Time after drug initiation)				
< 1 month	17 (23.0)	8 (47.1)	4 (23.5)	5 (29.4)
1-3 months	21 (28.4)	13 (61.9)	5 (23.8)	3 (14.3)
3-6 months	5 (6.8)	2 (40)	2 (40.0)	1 (20.0)
6-12 months	2 (2.7)	2 (100)	0	0
> 12 months	2 (2.7)	1 (50)	1 (50.0)	0

Table 2 Cutaneous adverse events in patients treated with EGFR Inhibitors

Outcome	Study Population (N=74)(%)	Afatinib (N=41)(%)	Gefitinib (N=20)(%)	Erlotinib (N=13)(%)
EGFR use				
Stop drug due to cutaneous adverse events	2 (4.3)	1 (50.0)	1 (50.0)	0
Decrease drug dose due to cutaneous adverse events	3 (6.3)	3 (100)	0	0

Table 3 Types and onset of cutaneous adverse events in patients treated with EGFR Inhibitors

PRIDE syndrome dermatologic adverse event	Medication				Onset of symptom after drug initiation, median (days)
	All (N=47) (%)	Afatinib (N=26) (%)	Gefitinib (N=12) (%)	Erlotinib (N=9) (%)	
Skin toxicities					
Xerosis	31 (65.9)	18 (58.1)	8 (25.8)	5 (16.1)	30 (7,365)
Papulopustular rash	20 (42.6)	11 (55.0)	5 (25.0)	4 (20.0)	29 (7,365)
Pruritus	10 (21.3)	6 (60.0)	3 (30.0)	1 (10.0)	75 (7,490)
Erythema	6 (12.8)	4 (66.7)	0	2 (33.3)	30 (14,150)
Acne	3 (6.4)	2 (66.7)	0	1 (33.3)	30 (6,30)
Other	12 (25.5)	8 (66.7)	3 (25.0)	1 (8.3)	30 (7,400)
Nail disorders					
Paronychia	27 (57.4)	21 (77.8)	4 (14.8)	2 (7.4)	60 (7,574)
Other	1 (2.1)	0	0	1 (100)	60 (60,60)
Hair disorders					
Trichomegaly (Eyelash growth)	2 (4.3)	1 (50.0)	1 (50.0)	0	195 (150,240)
Alopecia	4 (8.5)	1 (25.0)	1 (25.0)	2 (50.0)	195 (30,240)
Other	1 (2.1)	1 (100)	0	0	30 (30,30)
Others					
Mucositis	7 (14.9)	3 (42.9)	2 (28.6)	2 (28.6)	30 (30,150)

Table 4 Cutaneous adverse events in patients treated with EGFR Inhibitors and Tumor response

Cutaneous adverse events (N=74)	Responders N (%)	Non Responders N (%)	P-value
No PRIDE	12 (44.4)	15 (55.6)	0.001
PRIDE	38 (80.9)	9 (19.1)	

Table 5 Numbers of cutaneous adverse events in patients treated with EGFR Inhibitors and Tumor response

Number of cutaneous adverse events (N=47)	Responders N (%)	Non Responders N (%)	P-value
1 type	8 (21.1)	2 (22.2)	0.37
2 types	11 (29.0)	5 (55.6)	0.91
>2 types	19 (50.0)	2 (22.2)	0.31

Table 6 Types of cutaneous adverse events in patients treated with EGFR Inhibitors and Tumor response

Cutaneous adverse events	Tumor response		OR	95% CI	P-value
	Responders N (%)	Non Responders N (%)			
Skin toxicities					
- Papulopustule rash	17 (85.0)	3 (15)	3.61	0.94,13.82	0.05
- Acne	3 (100)	0	0.66	0.56,0.78	0.22
- Xerosis	24 (77.4)	7 (22.6)	2.24	0.79,6.35	0.12
- Pruritus	9 (90.0)	1 (10.0)	5.05	0.60,42.41	0.10
- Erythema	6 (100)	0	0.65	0.54,0.77	0.08
- Other	11 (91.7)	1 (8.3)	6.49	0.79,53.56	0.06
Nail disorders					
- Paronychia	23 (85.2)	4 (14.8)	4.26	1.27,14.27	0.01
- Other	1 (100)	0	0.67	0.57,0.79	0.49
Hair disorders					
- Trichomegaly (Eyelash growth)	2 (100)	0	0.67	0.57,0.79	0.32
- Alopecia	4 (100)	0	0.66	0.56,0.78	0.15
- Other	1 (100)	0	0.67	0.57,0.79	0.49
Others					
- Mucositis	5 (71.4)	2 (28.6)	1.22	0.22,6.80	0.82

Treatment

Patients with xerosis were treated with emollients (e.g., cream base, cream urea) with improvement in all patients. Papulopustular eruption was treated by medium-potency topical corticosteroids and oral doxycycline antibiotic 200 mg/day with good response. Trichomegaly was treated by eyelash trimming.

Discussion

This study found 47 of 74 patients (63.5%) with stage IV non-small cell lung cancer treated with erlotinib, gefitinib and afatinib presented at least one cutaneous adverse event, which was consistent with previous studies in Thailand[9,10], Asia, and Europe[7,8,14]. The most common cutaneous adverse events were xerosis (65.9%), consistent with previous studies in Thailand[9,10] but unlikely to other countries; Japan[4], Italy[7], America[8] that most common rash was papulopustular rash. It is because an EGFR inhibitor has inhibited the epidermal growth factor from being a barrier of epithelial layer of the skin that leads to xerosis. Moreover, some patients had received previous chemotherapy that was cytotoxic drugs resulting in alteration of the epithelial layer. Meanwhile, Thai people often shower with bar soaps in a tropical country. Nevertheless, there are no standard criteria to evaluate xerosis.

The average onset of xerosis, papulopustular rash, acne, and mucositis was 30 days; pruritus 75 days; paronychia and other nail disorders 60 days; trichomegaly (eyelash growth) and alopecia 6.5 months consistent with previous studies[4,6-10].

The afatinib group had the most presence and numbers of cutaneous adverse events (55.3%) because its pharmacokinetic and efficacy was better than others.

Two patients (4.3%) discontinued therapy due to PRIDE syndrome and three patients (6.3%) were prescribed a decreased dose of EGFR inhibitor. The others (89.4%) continued the same dose consistent with previous studies[4,8,15,16]. Therefore, PRIDE syndrome impacted EGFR inhibitors treatment in this study. The reason for discontinuation of the drug was the numbers and severity of cutaneous adverse events. Systemic doxycycline is the effective treatment.

Outcome about the association between demographic characteristics of the patients and cutaneous adverse events was inconsistent with previous studies reported that more drug dose tends to developed cutaneous adverse events[7] and elderly were likely to have xerosis[9]. However, it may be disturbed by small sample size and only afatinib had various drug doses (30 and 40 mg).

This study found the PRIDE syndrome had statistically significant association with tumor response and can support previous studies[4,6-9,11,12]. We also found papulopustular rash and

paronychia were associated with tumor responses.

The limitations of this study include single-center study leading to difficulty in the generalization, as data was collected from a single hospital. In addition, it is a retrospective study, with data collection from medical records leading to recall bias and incompleteness of the data. Moreover, the data was collected from patients who refer to dermatology clinic, therefore some of patients who developed cutaneous adverse events may have been missed.

Conclusion

Cutaneous adverse events due to EGFR inhibitors are common in Thais. The most common adverse events were xerosis. PRIDE syndrome had statistically significant association with tumor response, including papulopustular rash and paronychia, supporting PRIDE syndrome can be used as a marker of tumor's treatment outcome. The characteristics of cutaneous adverse events and onset of each cutaneous adverse event can be used in real life for advising and reassuring the patients to observe their skin side effects. Therefore, pulmonologists or oncologists can refer the cases to dermatology clinics, as soon as the cutaneous adverse events occur before it intervenes EGFR inhibitors use.

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