Target-Adverse Events and Fear of Cancer Progression, Anxiety, and Depression in Patients with Advanced Non-Small Cell Lung Cancer

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Research Article

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Abstract

Objective: To examine the difference in levels of fear of cancer progression (FoP), anxiety, depression between presence/absence of the target-adverse events (AEs); and to examine the differences in incidence rate of AEs and FoP, anxiety, and depression among three generations of EGFR-TKIs therapy (first, gefitinib and erlotinib [G1]; second, afatinib [G2]; third, osimertinib [G3]) in non-small-cell lung cancer (NSCLC) patients.

Methods: A cross-sectional study design. NSCLC patients (n=128) were recruited from a medical center in Taiwan. A set of structured questionnaires assessing AEs, FoP, anxiety and depression.

Results: Parts of AEs, such as photosensitivity, paronychia, and alopecia, exhibited significantly higher levels of FoP, anxiety, and depression. Less patients experienced AEs in the G3 group than those in the G1 or G2 group but still reported experiencing itching, dry skin with grade 3 severity. The incidence rates of mouth/throat sores, and cheilosis/cheilitis in the G2 group was significantly higher than those in the G1 or G3 group. The incidence rate of FoP, anxiety and depression were 13.8-26.3%, 23.8-40.4% and 16.7-42.1%, respectively.

Conclusions: The priorities of care among three generations of EGFR-TKIs in patients with NSCLC were established. FoP, anxiety and depression were present among different targeted therapies and require further attention.

1 Background

Lung cancer is one of the most life-threatening cancers worldwide. In Taiwan, the number of deaths due to lung cancer accounts for 19.22% (n = 9,235) of all cancer-related deaths (n = 48,037) in 2017 [1]. Approximately 50% of Asian patients with non-small-cell lung cancer (NSCLC) have mutations in epidermal growth factor receptor (EGFR), which are more than what have been accounted for in Caucasian patients (10% show EGFR mutations) [2]. A previous study that followed-up the use of first generation (gefitinib, erlotinib) EGFR- tyrosine kinase inhibitor (TKI) in patients with late-stage NSCLC in Taiwan for 3 years found that the survival rate significantly increased and mortality significantly decreased with the use of this therapy [3]. However, patients treated with first (gefitinib and erlotinib) and second (afatinib) generation of EGFR TKIs will eventually develop clinical resistance and up to 60% of these resistance patients have acquired EGFR exon 20 (T790M) mutations [4]. The third generation (osimertinib) of EGFR-TKIs therapy can then be chosen to continuously control the disease with the benefit of achieving improved central neural system penetration [5–7]. Thus, the three generations of EGFR-TKIs have now become one of the predominant anti-cancer therapies for patients with lung cancer.

However, target-adverse events (AEs) such as skin rash and xerosis/dry skin are associated with EGFR-TKI use [8, 9]. In fact, targeted therapy was stopped in 10% of the patients who developed such adverse-events [10]. Recent studies have reported that patients treated with osimertinib treatment have better progression-free survival [11] and lower frequency of grade 3 or 4 AEs (rash, pruritus, xerosis/dry skin, and paronychia) than patients treated with gefitinib, erlotinib [11], or afatinib [12]. These target adverse effects were assessed by professionals. To improve the quality of personal, professional, and organizational relationships, patient-center care should also give consideration to patient voice during assessment in clinical settings [13]. Additionally, a review article also pointed out the gaps of patient voice concerning adverse-events from EGFR inhibitors [14]. Thus, the perspectives of both patients and professionals regarding AEs will be simultaneously assessed in this study.

According to the middle-range theory of unpleasant symptoms, physiological and psychological factors can simultaneously influence an individual's health status [15]. There is evidence which indicates that skin toxicity negatively affects patients' emotions, life functioning, and quality of life [9, 16]. Thus, patients with NSCLC receiving targeted therapies, that had AEs (e. g., acneiform eruption/ acne, pruritus/ itching, dry skin/ skin dryness, paronychia, hyperpigmentation, photosensitivity, alopecia/ hair loss, and hypertrichosis, mouth/throat sores, and cheilosis/cheilitis) and fear of cancer progression (FoP), anxiety, and depression were selected as physiological and psychological factors in this study. In relation to physiological factors, previous studies on the differences among different EGFR-TKI therapies focused more on patients treated with gefitinib, erlotinib, and afatinib. However, few studies explored some parts of the adverse events such as acneiform eruption, pruritus, dry skin, paronychia [9, 17] and diarrhea [18, 19]. Furthermore, one study reported that a lower incidence rate of AEs with grade 3 or higher was found in osimertinib-treated patients than in patients treated with the gefitinib, erlotinib, and afatinib [11]. Previous literature more often discussed the overall quality of life with targeted therapy patients reporting some degree of psychological distress, but seldom discussed the details of psychological status in patients treated with EGFR-TKI therapies [9, 17]. Regarding psychological factors, few studies examine FoP, anxiety, and depression among different EGFR-TKI therapies. FoP, anxiety, and depression are common experiences for cancer patients [20, 21] and FoP is also considered as the most prevalent unmet needs (14 to 42%) [20, 22], which will be further explored in the current study.

To our knowledge, few studies have simultaneously examined the difference in FoP, anxiety, depression between presence/absence of the AEs; as well as the differences among the three generations of EGFR-TKIs with/in consideration of both physiological and psychological factors. We hypothesized that patients with NSCLC in three generations of EGFR-TKIs (first [G1], gefitinib and erlotinib; second [G2], afatinib; third [G3], osimertinib) might be suffering from AEs causing them to have higher levels of FoP, anxiety and depression; and that patients might be experiencing different incidence rates of AEs. The results obtained in this study may indicate the need for special clinical care for the benefit of ameliorating patient health status.

2 Methods

2.1 Design

This was a prospective, comparative, cross-sectional study, and was part of a larger study on patients with NSCLC treated with EGFR-TKIs. A purposive sampling was used. For data collection, patients' AEs were assessed by the National Cancer Institute Common Toxicity Criteria and Adverse Events (CTCAE v

4.03) and patient-reported outcome measures (PRO-CTCAE 1.0). Patients' FoP was assessed by the Fear of Progression Questionnaire-Short Form (FoP-Q-SF) [23] and anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS), as described in detail below

2.2 Participants

Patients were recruited from an oncology-dermatology outpatient setting of a medical center in Northern Taiwan from October 01, 2018 to December 12, 2019. Eligible patients (i) were ≥ 20 years old; (ii) had been diagnosed with NSCLC at stage IIIb or IV; (iii) had received oral EGFR-TKI treatment (gefitinib, erlotinib, afatinib, or osimertinib) for at least 2 weeks; (iv) had adverse skin-related events and were receiving treatment in an oncology-dermatology outpatient setting; and (v) were able to communicate in Mandarin or Taiwanese. All patients understood the purpose of this study and signed an informed consent form of participation. This study was approved by the Institutional Review Board of the medical center.

2.3 Measures

2.3.1 Target-Adverse Events (AEs)

AEs were assessed using the Chinese version of CTCAE v 4.03 and PRO-CTCAE 1.0. Nine CTCAE 4.03 items (acneiform eruption, pruritus, dry skin, hyperpigmentation, photosensitivity, paronychia, alopecia, hypertrichosis, and oral mucositis) [13] and six PRO-CTCAE 1.0 items (acne, itching, skin dryness, hair loss, mouth/throat sores, and cheilosis/cheilitis) were most commonly associated with target-adverse event measures [24]. The severity grade of CTCAE 4.03 was ranked as grade 1 (mild) to 5 (death) according to the descriptions of each adverse event [13]. Further, PRO-CTCAE 1.0 was used to capture the experience of the patient in respect of the AEs, and their severity (none to very severe) and frequency (never to almost constantly) were assessed [24]. The incidence rate of each adverse event with any severity grade was calculated in this study.

2.3.2 FoP, Anxiety, and Depression

As mentioned previously, patients' FoP was assessed using the FoP-Q-SF [23]. This scale consists of 12 items which are scored from 1 (never) to 5 (very often) and a score ranging from 12 to 60. The higher scores indicate more FoP. The cut-off point of dysfunctional level of FoP is a score of 34 or above [25]. The Cronbach's alphas of FoP-Q-SF was 0.89 in the current study.

Patients' anxiety and depression were measured by the Hospital Anxiety and Depression Scale. This scale consists of 14 items: 7 items for anxiety subscale and 7 items for depression subscale. The scores range from 0 to 21 for each subscale and higher scores reflect more anxiety and depression. The scores ranging from 0 to 7 indicate non-case and 8 to 21 indicate borderline cases or cases of anxiety or depression [26]. The Cronbach's alphas of anxiety and depression were 0.84 and 0.75, respectively in the current study.

2.3.3 Background Information Form

The Background Information Form of the participants included sex, age, NSCLC stage, treatment time of targeted therapy (days), duration of outpatient treatment in dermatology (days), generation(s) of EGFR-TKIs, and Eastern Cooperative Oncology Group (ECOG) Performance Status, which was used to assess the performance status of the patients and grade them from 1 (fully active) to 5 [27].

2.4 Statistical Analysis

SPSS version 24.0 software was used for the data analysis. Descriptive statistics such as mean, standard deviation (SD), number, and frequency were used to describe the background information of the participants, incidence rate, and severity of the AEs, FoP, anxiety, and depression. Since the scores were not normally distributed, we used nonparametric analysis methods. Thus, the Mann-Whitney U test was used to compare the differences in FoP, anxiety, depression between presence/absence of AEs. We analyzed the differences in incidence rate of the AEs, FoP, anxiety, and depression among the three generations of EGFR-TKIs using chi-square and Fisher's exact test [28].

3 Results

3.1 Subject Characteristics

A total of 140 patients were initially approached, but 12 patients were too tired to finish the questionnaires or did not have time. Thus, data was collected from 128 patients for the final analysis (response rate = 91.4%).

Most patients (44.5%) had received the first-generation EGFR-TKIs (gefitinib, erlotinib; G1), and 32.8% and 22.7% had received the second- (afatinib; G2) and third-generation (osimertinib; G3) EGFR-TKIs, respectively. Most of the patients were female in the G1 (71.9%) and G3 (75.9%) groups and the percentage (50%) of male and female was equal to the G2 group. The mean age was 67.6 (SD=10.9), 61.2 (SD=10.3), and 64.6 (SD=11.7) in the G1, G2, and G3 groups, respectively. The majority of patients (92.9%~100%) were stage IV in three groups and the treatment time of targeted therapy (days) and ECOG performance status were similar in three groups (Table 1).

3.2 Comparison of the Incidence Rates of the AEs

From the perspective of the professionals, the incidence rates of photosensitivity ($p = 0.0001$), hypertrichosis ($p = 0.009$), and oral mucositis ($p = 0.013$) in the G3 group were significantly lower than those in the G1 and G2 groups. From the perspective of the patients, the incidence rates of acne ($p = 0.002$), mouth/throat sores ($p = 0.004$), and cheilosis/cheilitis ($p = 0.02$) in the G3 group were significantly lower than those in the G2 group (Table 2).

3.3 The difference in FoP, anxiety, depression between presence/absence of the target-adverse events

Patients with photosensitivity had significantly higher (worse) levels in FoP and anxiety. Patients with alopecia had significantly higher levels in anxiety. Patients with paronychia had significantly higher levels in depression (Table 3).

3.4 Comparison of the Incidence Rates of FoP, Anxiety and Depression

The incidence rates of dysfunctional FoP in the G1, G2, and G3 with borderline cases or cases were 26.3%, 26.3%, and 13.8%, respectively. The incidence rates of anxiety with borderline cases or cases in the G1, G2, and G3 were 40.4%, 23.8%, and 24.1%, respectively. Finally, the incidence rates of depression in the G1, G2, and G3 with borderline cases or cases were 42.1%, 16.7%, and 27.6%, respectively. The incidence rates of depression with borderline cases or cases ($p = 0.023$) in the G1 group were significantly higher than those in the G2 groups (Table 4).

4 Discussion

This is the first study that has simultaneously examined the difference in levels of FoP, anxiety, depression between presence/absence of the AEs and the differences in the incidence rate of AEs and FoP, anxiety, and depression among three generations of EGFR-TKIs therapy (first, gefitinib and erlotinib [G1]; second, afatinib [G2]; third, osimertinib [G3]) in patients with NSCLC.

First, our findings are in accordance with those of previous studies [9, 17], assessments of AEs from both professionals' and patients' perspectives, as the major four AEs in our study were also acneiform eruption/acne, itching, dry skin/skin dryness, and paronychia. Further, the aforementioned studies also focused on patients treated with gefitinib, erlotinib, and afatinib. Although this study included some patients treated with osimertinib, the results were similar. From the patients' perspective, less patients (37.9%) reported acne in the G3 group than in the G2 group in our current study but more than half of them still experienced the other three AEs, including itching, dry skin/skin dryness, and paronychia. Thus, patients should be taught how to self-care such as with the use of menthol-based anti-pruritic moisturizers and conservative nail clipping for paronychia [29]. Moreover, in a previous study, a lower incidence rate of AEs (acne, pruritus, xerosis/dry skin, and paronychia) with grade 3 or higher was found in osimertinib-treated patients (0–1%) than in patients treated with the first and second generations of EGFR-TKIs [11]. Chu et al performed a study in Taiwan and observed that the four adverse events with grade 3 or higher was in the range 0–15% [12], similar to that in our study. Here, we observed itching (3.3%) and dry skin (10%) with grade 3 severity, which may result in the interruption the treatment or reduction of dosage [14]. Thus, even patients undergoing osimertinib therapy should also further discuss AEs and be advised to report adverse events to their case managers as soon as possible. In addition, our study reveals that the highest incidence rate of photosensitivity were found in patients with gefitinib, erlotinib therapy (54.4%) and this rate was approximately 4 times higher than that of patients with osimertinib therapy (13.8%). Thus, these results indicate that when patients are treated with gefitinib and erlotinib, the importance of using hats, protective clothing and sunblock with sun protection factor > 30 should be conveyed in clinical settings [30, 31]. Finally, our study found that AEs assessed by PRO-CTCAE 1.0 is strongly recommended for use in clinical settings, as it echoed the CTCAE v 4.03 assessment by professionals in this study. However, there were still some events such as photosensitivity that was too difficult to consider for the comparison of the severity of CTCAE. For instance, the question that was asked about photosensitivity in the PRO-CTCAE was "In the last 7 days, did you have any increased skin sensitivity to sunlight?" Therefore, we didn't include this question in this study.

From the professionals' and patients' perspectives, we found that the other major findings were gastrointestinal system-related adverse events. Higher incidence rates of mouth/throat sores, and cheilosis/cheilitis were found in patients in the G2 group and were 2 or 3 times higher than in patients in the G1 and G3 group, which a previous study only reported diarrhea symptom [18]. The incidence rate of diarrhea is reportedly higher in patients who receive afatinib therapy than in those receiving gefitinib or erlotinib therapy [18]. These results indicate that patients receiving afatinib therapy should have their diarrhea symptoms closely examined and should consider the possibility of dehydration, electrolyte imbalance, and infection [32]. Therefore, patients undergoing afatinib therapy are also recommended to have their gastrointestinal system routinely assessed at every appointment, and they should be advised to perform appropriate mouth care (4–6 times mouthwash, if necessary, increasing the frequency of the mouthwash, up to 1 hour) [32] and to drink enough water (8–10 glasses) even if they only have grade 1 diarrhea symptoms (number < 4 times) [33].

Patients with NSCLC who received different targeted therapy suffered some skin toxicity which partly caused them to have higher levels of FoP, anxiety, depression. Similar to previous studies, the results showed that the patients' physiological and psychological indicators were simultaneously affected, and that the physiological side effects affect patients' psychological distress, body image or daily life function [9, 15, 16]. Patients experienced FoP, anxiety, depression during cancer treatment, which echoes to past studies [34, 35]. In the current study, the incidence rates of anxiety in the G1 group with borderline cases or cases were over 40.4%, while the rate of depression was 42.1%. These findings were lower than those in a previous study [36], showing that 43.5% and 57.1% of lung cancer patients were identified with anxiety and depression [36]. This difference may be due to the fact that most patients (72.1%) received chemotherapy whereas 13% received targeted therapy [36], which has been documented to be better tolerated than chemotherapy [37]. In addition, in our study, we also found that patients' anxiety, depression and FoP in G2 and G3 group were in the range from 13.8 to 27.6%. The lower incidence rate might be supported by previous studies showing that the incidence rate of psychological distress may decrease after diagnosis or cancer treatment and then become stable [34, 35]. Forty-five percent of patients in the G2 group and 96.5% of patients in the G3 group were not considered for first-line treatment. In other words, more patients might have undergone previous anti-cancer therapies suggesting that their FoP, anxiety, and depression might have decreased after initial cancer treatment and explaining why more patients experienced severe anxiety and depression in the G1 group. 61.4% of those in the G1 group were used for first-line treatment in this study. Furthermore, another reason might be that female patients are more prone to report anxiety and depression [38, 39]. 70% of the patients in the G1 group were female. This suggests that patients have some similar degree of FoP, anxiety, depression while receiving different targeted

therapies, even though patients had lower severity of some adverse events. Thus, in clinical settings, this psychological issue should not be overlooked. Patients should be routinely assessed and if necessary, anxiety and depression borderline cases or cases, and dysfunctional FoP cases should be referred to further care.

5 Conclusions

The major findings suggest that patients receiving osimertinib therapy may have lower frequency or severity of acneiform eruption/acne, photosensitivity, hypertrichosis, mouth/throat sores, and cheilosis. However, patients still reported itching, dry skin, and grade 3 severity; therefore, these events should be addressed. Furthermore, patients undergoing afatinib therapy should not ignore gastrointestinal system assessment, as these are manageable adverse events to improve their quality of life. Finally, persistent FoP, anxiety and depression in patients with targeted therapy should not be ignored and needs to be further explored.

6 Study Limitations

Since this was a cross-sectional data analysis, there was limited understanding of the time-related changes in the AEs, FoP, anxiety and depression in patients with NSCLC receiving EGFR-TKIs. Even though our study included PRO-CTCAE 1.0 to consider the perspective of patients, qualitative research is required for making further recommendations.

7 Clinical Implication

Our results suggest that health care professionals should address the priorities of care among three generations of EGFR-TKIs in patients with NSCLC. The screening results of FoP, anxiety and depression calls for routine screening and further care.

Declarations

Funding

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Conflict of Interest

The authors declare that they have no conflict of interest.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability:

N/A

Authors' contributions

Y. H. Lee and C. C. Yu designed and directed the project; C. C. Yu and J. C. Chan collected the data; Y. H. Lee and C. C. Yu analysed final data; C. Y. Chu and Y. H. Lai were involved in planning and supervised the work; Y. H. Lee drafted the manuscript and Y. J. Chen and H. T. Hsu contributed to designed the tables. All authors discussed the results and commented on the manuscript.

Ethics approval

Institutional Review Board approval of National Taiwan University Hospital, Taipei, Taiwan (20180705RINB)

Consent to participate

For the research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants

Consent for publication

N/A

Conflict of Interest

None to declare.

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Tables

Table 1 Patients background information (N=128)

Variables	G1 ^a (n=57/128; 44.5 %)	G2 ^b (n=42/128; 32.8 %)	G3 ^c (n=29/128; 22.7%)
Gender			
Male	16 (28.1)	21 (50.0)	7 (24.1)
Female	41 (71.9)	21 (50.0)	22 (75.9)
Age (years)	67.6 (10.9)	61.2 (10.3)	64.6 (11.7)
Stage			
III	3 (5.3)	3 (7.1)	0 (0.0)
IV	54 (94.7)	39 (92.9)	29 (100.0)
Treatment time of targeted therapy (days)	452.7 (610.9)	404.1 (412.5)	428.7 (393.6)
Previous treatment			
Yes	50 (38.6)	19 (45.2)	1 (3.4)
No	35 (61.4)	23 (54.8)	28 (96.6)
ECOG Performance Status	1.3 (0.5)	1.1 (0.4)	1.3 (0.7)

Note^aG1^a: indicates the first-generation EGFR-TKIs (Gefitinib or Erlotinib); G2^b: indicates the second-generation EGFR-TKIs (Afatinib);

G3^c: indicates the third generation EGFR-TKIs (Osimertinib).

Note^aG1^a: indicates the first generation EGFR-TKIs (Gefitinib or Erlotinib); G2^b: indicates the second generation EGFR-TKIs (Afatinib); G3^c: indicates the third generation EGFR-TKIs (Osimertinib); chi-square and Fisher's exact test, *p<0.05[†]p<0.01[‡]Bonferroni's method

Table 3 The difference in FoP, anxiety, depression between presence/absence of the target-adverse events

Table 2 Comparison of the incidence rate of the target-adverse events assessed by CTCAE 4.03 and PRO-CTCAE 1.0

CTCAE 4.03 (Professionals' perspective)											PRO-CTCAE 1.0 (Patients' perspective)				
Adverse Event	G1 ^a (n=57)		G2 ^b (n=42)		G3 ^c (n=29)		χ ²	p	†Post hoc	Adverse Event	G1 ^a (n=57)		G2 ^b (n=42)		G3 ^c (n=29)
	n (%)		n (%)		n (%)						n (%)		n (%)		
	All Grade	Grade 3	All Grade	Grade 3	All Grade	Grade 3					All Response	Very Severe	All Response	Very Severe	
Acneiform eruption	47	5	34	2	16	0	10.74	0.082	—	Acne	36	1	34	0	11
	(82.5)	(8.8)	(81.0)	(4.8)	(55.2)	(0)					(63.2)	(1.8)	(81.0)	(0)	(37.9)
Itching	51	8	40	4	24	1	5.71	0.46	—	Itching	51	3	40	1	21
	(89.5)	(14.0)	(95.2)	(9.5)	(82.2)	(3.4)					(89.5)	(5.3)	(95.2)	(2.4)	(72.4)
Dry skin	51	4	37	3	22	3	4.02	0.68	—	Skin dryness	52	2	35	0	23
	(89.5)	(7.0)	(88.1)	(7.1)	(75.9)	(10.3)					(91.2)	(3.5)	(83.3)	(0)	(79.3)
Hyperpigmentation	35	—	27	—	13	—	2.94	0.58	—						
	(61.4)		(64.3)		(44.8)										
Photosensitivity	31	0	12	0	4	0	20.35	0.0001**	G3<G2<G1						
	(54.4)	(0)	(28.6)	(0)	(13.8)	(0)									
Paronychia	36	2	36	2	22	0	21.25	0.001**	G1<G2						
	(63.2)	(3.5)	(85.7)	(4.8)	(75.9)	(0)									
Alopecia	23	—	14	—	5	—	7.08	0.11	—	Hair loss	21	0	16	0	5
	(40.4)		(33.4)		(17.2)						(36.8)	(0)	(38.1)	(0)	(17.2)
Hypertrichosis	41	—	33	—	13	—	11.78	0.009**	G3<G2						
	(71.9)		(78.6)		(44.8)										
Oral mucositis	15	1	23	0	6	0	13.36	0.013*	G1,3<G2	Mouth/throat sores	10	0	18	0	5
	(26.3)	(1.8)	(54.8)	(0)	(20.7)	(0)					(17.5)	(0)	(42.9)	(0)	(17.2)
										Cheilosis/cheilitis	14	0	18	0	5
											(24.6)	(0)	(42.9)	(0)	(17.2)

CTCAE 4.03	FoP				Anxiety			Depression		
	Mean (SD)	Mean Rank	p	p	Mean (SD)	Mean Rank	p	Mean (SD)	Mean Rank	p
	n									
Acneiform eruption										
No	31	27.2 (9.7)	61.5	.607	4.2 (3.7)	57.0	.192	6.3 (4.4)	71.3	.242
Yes	97	28.0 (9.3)	65.5		5.4 (4.0)	66.9		5.2 (3.7)	62.3	
Itching										
No	13	23.5 (7.2)	48.7		3.0 (2.3)	46.0		5.1 (4.0)	60.2	
Yes	115	28.3 (9.5)	66.3	.105	5.3 (4.1)	66.5	.057	5.5 (3.8)	65.0	.655
Dry skin										
No	18	24.7 (5.9)	52.7		4.8 (3.6)	62.6		4.9 (3.6)	60.1	
Yes	110	28.3 (9.7)	66.4	.146	5.2 (4.1)	64.8	.809	5.6 (3.9)	65.2	.584
Hyperpigmentation										
No	53	26.9 (9.0)	61.2		4.5 (3.7)	59.4		5.5 (4.2)	63.4	
Yes	75	28.4 (9.6)	66.8	.402	5.5 (4.2)	67.7	.240	5.5 (3.6)	65.3	.773
Photosensitivity										
No	81	26.1 (8.5)	58.0		4.3 (3.8)	56.6		5.3 (4.0)	62.3	
Yes	47	30.8 (10.0)	75.6	.010	6.5 (4.0)	78.1	.001	5.8 (3.6)	68.3	.376
Paronychia										
No	34	27.1 (8.1)	62.8		4.8 (3.8)	61.6		4.0 (3.0)	50.6	
Yes	94	28.1 (9.8)	65.1	.756	5.2 (4.1)	65.6	.591	6.0 (4.0)	69.5	.011
Alopecia										
No	86	26.8 (8.4)	61.2		4.5 (3.7)	58.6		5.1 (3.8)	60.4	
Yes	42	29.9 (10.8)	71.3	.147	6.4 (4.3)	76.5	.010	6.3 (3.9)	72.4	0.91
Hypertrichosis										
No	41	26.2 (8.2)	57.9		4.6 (4.0)	59.2		4.9 (3.7)	58.9	
Yes	87	28.5 (9.8)	67.6	.168	5.3 (4.0)	67.0	.267	5.8 (3.9)	67.1	.243
Oral mucositis										
No	84	29.8 (9.3)	60.6		4.8 (4.1)	61.2		5.4 (3.9)	63.7	
Yes	44	29.7 (9.3)	71.9	.101	5.6 (3.7)	70.7	.168	5.6 (3.7)	66.1	.726

Note: The Manne-Whitney U test was used to compare the differences between the two groups.

Table 4 Comparison of FoP, anxiety and depression incidence rates (N=128)

	G1 ^a (n=57)	G2 ^b (n=42)	G3 ^c (n=29)	χ ²	p	†Post hoc
Variables (theoretical scores)	n (%)	n (%)	n (%)			
Fear of Progression (FoP)						
Non-dysfunctional FoP (12-33)	42 (73.7)	31 (73.8)	25 (86.2)	1.94	0.378	
Dysfunctional FoP (34-60)	15 (26.3)	11 (26.3)	4 (13.8)			
Anxiety (0-21)						
Non-cases (0-7)	34 (59.6)	32 (76.2)	22 (75.9)	3.96	0.138	
Borderline cases or cases (8-21)	23 (40.4)	10 (23.8)	7 (24.1)			
Depression (0-21)						
Non-cases (0-7)	33 (57.9)	35 (83.3)	21 (72.4)	7.53	0.023*	G2<G1
Borderline cases or cases (8-21)	24 (42.1)	7 (16.7)	8 (27.6)			

Note: ^aFoP was measured by (FoP-Q-SF); Anxiety and depression were measured by HADS; G1^a: indicates the first generation EGFR-TKIs (Gefitinib or Erlotinib); G2^b: indicates the second generation EGFR-TKIs (Afatinib); G3^c: indicates the third generation EGFR-TKIs (Osimertinib); chi-square and Fisher's exact test, *p<0.05, **p<0.01, †Bonferroni's method