Observational Study

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Effects of tyrosine kinase inhibitor therapy on skin toxicity and skin-related quality of life in patients with lung cancer

An observational study

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Abstract

Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) therapy is the primary treatment option for patients with non-small cell lung cancer (NSCLC). However, one of the major adverse effects associated with this therapy is skin toxicity, which impacts the patient's quality of life. This study aimed to describe the severities and locations of skin toxicity, and to analyze their association with the quality of life in patients with advanced NSCLC who received EGFR-TKI therapy as first-line treatment.

This cross-sectional and correlation study was conducted at a tertiary medical center in northern Taiwan between July 2015 and March 2016. Skin toxicity was assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). The Skindex-16 scale was used to measure the skin disease-related quality of life.

A total of 146 NSCLC patients who received EGFR-TKI therapy within the first 3 months of diagnosis were included in this study; 93.2% of these patients experienced skin toxicities. Approximately 70% of the patients developed xerosis and pruritus, while 50% had papulopustular eruptions and paronychia. The mean skin symptom impact score was 5.38 (standard deviation = 2.65). The skin-related quality of life varied widely among the participants but remained acceptable (mean score = 13.96, standard deviation = 16.55). Skin symptoms correlated significantly with poor quality of life ($r = 0.50$, $P < .001$). Younger patients and those treated with afatinib were the most affected, reporting the poorest quality of life. Patients who required EGFR-TKI dose reduction had experienced more severe skin symptoms than had patients who did not require it (7.35 vs 5.01, $P < .001$).

Skin toxicity related to EGFR-TKI treatment impacts the quality of life in patients with NSCLC. During the treatment period, skin assessment and tailored management should be incorporated into the daily care plan.

Abbreviations: ECOG PS = Eastern cooperative oncology group performance status, EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor, NCI-CTCAE = National Cancer Institute- Common Terminology Criteria for Adverse Events, NSCLC = non-small cell lung cancer, SD = standard deviation, SRQOL = skin-related quality of life, SSI = skin symptom impact.

Keywords: advanced non-small cell lung cancer, dermatological side effects, quality of life, skin toxicity, targeted therapy

1. Introduction

Lung cancer is a highly prevalent and deadly global disease.[1–3] Approximately 70% to 75% of patients newly diagnosed with lung cancer are already at an advanced disease stage (ie, stage 3B or 4).[3] Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) including gefitinib, erlotinib, and afatinib have recently emerged as major therapeutic agents for treating advanced non-small cell lung cancer (NSCLC).[4–6] EGFR-TKIs block the activation of downstream EGFR signaling, resulting in cancer cell death. However, these agents can damage normal skin cells and cause skin toxicities such as xerosis, pruritus, acneiform or papulopustular eruption, nail changes, and paronychia.[7,8] The incidence of skin toxicity has been estimated to range between 66.5% and 91%, with most classified as grade 1 or 2 toxicity.[4,9,10] Skin toxicity has been identified as the most debilitating factor in patients receiving EGFR-TKI therapy.[11]

A meta-analysis that compared patients receiving chemotherapy to those receiving EGFR-TKIs found that the latter generally experience a better quality of life,[5] but may develop severe skin rashes that can lead to poor skin-related quality of life (SRQOL).[9] The 'symptom' and 'emotion' domains of the health-

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related quality of life are also impaired in patients treated with EGFR-TKIs.[12] Therefore, it is important that patients are made aware of skin-related adverse effects before initiating EGFR-TKI therapy, and are provided with a comprehensive assessment and early treatment of any skin-related symptoms that arise.

Understanding the effects of skin toxicity on the quality of life can provide a reference for clinical professionals who manage patients receiving EGFR-TKI therapy, as well as an empirical basis for the development of guidelines to enhance the quality of life of these patients.[13] Therefore, this study aimed to examine

(1) the skin toxicity and SRQOL,
(2) association between skin toxicity and SRQOL, and
(3) effect of EGFR-TKI dosage reduction on skin toxicity in patients with NSCLC receiving EGFR-TKI therapy.

2. Materials and methods

2.1. Study design and patients

This was a cross-sectional study that was conducted in the outpatient clinic of the Departments of Chest Medicine and Oncology at a medical center in northern Taiwan. Patients included in the study were those who

(1) were newly diagnosed with advanced NSCLC,
(2) received treatment with gefitinib, erlotinib, or afatinib as the first-line therapy within the first 3 months,
(3) were aged >18 years,
(4) had not undergone surgical resection or chemotherapy, and
(5) provided written consent.

Patients with lung cancer recurrence and those who had a second primary cancer were excluded from the study.

2.2. Procedure

Prior to the formal study, the first author and a clinical skin specialist performed a skin toxicity assessment in five patients receiving EGFR-TKI therapy, based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 skin toxicity severity grading, to confirm inter-observer reliability. These five patients were not included in the actual analysis cohort. Formal data collection was performed between July 2015 and March 2016. Patients who met the inclusion criteria were invited to participate in the study. The severity and location of their skin symptoms were graded by the first author using the NCI-CTCAE in an examination room immediately after study participants completed their questionnaires. This study was approved by the Institutional Review Board of the hospital (approval number 104–2200B). Data collection commenced after obtaining written consent from the participants. Patients were guaranteed the option to withdraw from the survey at any time, and were informed that all their provided information would be kept confidential and used only for academic purposes. Data were processed anonymously to avoid the divulging of information and to protect the privacy rights of the participants.

2.3. Questionnaires

2.3.1. Skin symptoms. Skin symptoms were assessed for severity, location, and impact. Four common symptoms of skin toxicity, namely, papulopustular reaction, paronychia, xerosis (skin dryness), and pruritus (itching), were assessed using the NCI-CTCAE version 4.03 and graded with scores of 1 to 4 based on severity. For example, grade 1 pruritus included mild or localized symptoms for which topical intervention was indicated, while grade 2 was characterized by moderate or widespread pruritus that involved skin changes from scratching, required oral medication, and limited instrumental activities of daily living. Grade 3 included symptoms that were serious and constant (but not immediately life-threatening) that led to hospitalization or an extended hospital stay, resulted in limited self-care activities of daily living or sleep, and required oral corticosteroid or immunosuppressive therapy. Grade 4 symptoms were life-threatening and required emergency treatment. Skin toxicity locations were divided into 5 regions: the scalp, face, limbs (arms and legs), fingers, and trunk (back, chest and belly). The skin symptom impact (SSI) score for each patient was calculated by combining the severity grading and location of symptoms to determine the overall impact of skin toxicity. The range of the SSI score was 0 to 20, with a higher score indicating a higher impact. For example, if a patient experienced grade 2 xerosis on the limbs and 1 grade papulopustular reaction on the face, the SSI score was 7 (2 symptoms, 2 locations, and 3 grades).

2.3.2. SRQOL. The Chinese version of the Skindex-16 scale was used to measure the SRQOL. The questionnaire comprised of 16 questions covering the symptoms, emotions, and functioning domains of the quality of life. Each question was scored from 0 (never bothered) to 5 (always bothered), and the scores were subsequently converted into linear percentages with 100% indicating a full score; a higher score indicated a poorer quality of life. This scale has been validated and shown to have good reliability.[14,15] In this study, the internal consistency reliability was good, with a Cronbach's alpha value of 0.96.

2.3.3. Basic data. The collected data included sex, age, physical function (Eastern Cooperative Oncology Group performance status [ECOG PS]), EGFR-TKI regimen and dose, treatment duration (days), and whether or not the EGFR-TKI dosage had been reduced during the treatment process.

2.4. Statistical analysis

Data were analyzed using the SPSS Statistics 22.0 software (IBM, Armonk, NY). Descriptive data including mean, standard deviation (SD), frequencies, and percentages were used to estimate the distribution of the data. Group differences were evaluated using the independent sample t-test or one-way analyses of variance for continuous variables, followed by pairwise comparisons for significant results. The chi-square test was used to examine group differences between categorical variables. The statistical significance level was set at $P < .05$.

3. Results

The study originally included 148 patients; however, one patient who required immediate chest ultrasound-guided examination owing to breathing difficulties, and was too weak to complete the questionnaire, was excluded from the study, as was another patient who no longer wished to participate. Thus, the final analysis evaluated data from 146 patients. Most participants were women (n = 95, 65.1%) with a mean age of 65.4 years (SD: 12.1) and stage IV disease (n = 131, 89.7%). The ECOG PS score was 0 in most patients (n = 108, 74%), indicating good physical

Table 1

Basic characteristics of the study patients (N = 146).

Variables	Mean	SD	n	%
Age	65.4	12.1		
Treatment Duration (d)	59	28.7		
Sex (female)			95	65.1
Marital status (married)			106	72.6
Education (high school and above)			45	30.8
Smoker			41	28.1
Employed			73	50
Stage				
IIIB			15	10.3
IV			131	89.7
ECOG PS				
0			106	72.6
1			29	19.9
2			8	5.5
3			3	2.1
Regimen				
Gefitinib (250 mg)			32	21.9
Erlotinib (150 mg)			30	20.5
Erlotinib (100 mg)			1	0.7
Afatinib (40 mg)			74	50.7
Afatinib (30 mg)			9	6.2
Dose Reduction				
No			123	84.2
Yes			23	15.8
Gefitinib			2	8.7
Erlotinib			3	13.0
Afatinib			18	78.3

ECOG PS = Eastern cooperative oncology group performance status, SD = standard deviation.

function status. Afatinib was the most frequently administered therapeutic agent (n = 83, 56.8%), followed by gefitinib (n = 32, 21.9%), and erlotinib (n = 31, 21.3%). The mean duration of the EGFR-TKI therapy was 59 days (SD: 28.7); 23 patients (15.8%) required dose reduction because of skin toxicity (Table 1).

Overall, 136 patients (93.2%) experienced grade ≥1 skin toxicity. The incidences of the four types of symptoms (grade ≥1) were as follows: xerosis (74.7%), pruritus (71.2%), papulopustular eruption (56.8%), and paronychia (55.5%). In terms of location, skin symptoms mostly appeared on the fingers (n = 81, 55.5%), followed by the face (n = 73, 50%), limbs (n = 60, 41.1%), trunk (n = 53, 36.3%), and scalp (n = 48, 32.9%). The SSI scores ranged from 0 to 12 with a mean score of 5.38 (SD: 2.65), while the Skindex-16 scores ranged from 0 to 82 with a mean score of 13.96 (SD: 16.55) (Table 2).

Age showed a negative correlation with both the SSI (r = -0.29, $P < .001$) and SRQOL (r = -0.29, $P < .001$) scores. Patients in the afatinib group had a higher SSI score (F = 12.29, $P < .001$) and poorer SRQOL score (F = 3.978, $P = .021$) compared to those in the gefitinib group (post-hoc Scheffe test). The SSI and SRQOL scores showed no associations with treatment duration, sex, marital status, education level, smoking, employment status, stage, or ECOG PS (Table 3).

Patients with skin toxicity symptoms other than xerosis experienced poor SRQOL. Skin symptoms appearing on the scalp (t = -2.09, $P = .04$), face (t = -3.95, $P < .001$), and fingers (t = -2.84, $P = .005$) were associated with poor SRQOL. The SSI score was negatively correlated with the SRQOL (r = 0.50, $P < .001$) (Table 4).

Skin toxicity symptoms appeared on the scalp in 56.5% of the patients in the dose reduction group, compared to 28.5% of those in the non-dose reduction group ($\chi^2 = 5.70$, $P = .02$). The SSI was significantly higher in the dose reduction group than in the non-dose reduction group (t = -4.09, $P < .001$), whereas the SRQOL was poorer in the former than in the latter (t = -2.88, $P = .008$) (Table 5). Comparisons between the dose reduction and non-dose reduction groups for each type of EGFR-TKI are shown in Table 6. In the afatinib group, patients who required dose reduction had higher SSI scores (7.61 vs 5.48) and poorer SRQOL scores (28.87 vs 13.02) than did those in whom doses were not reduced. No significant differences between patients who underwent dose reductions and those who did not were observed in the other treatment groups.

4. Discussion

In this study, 93.2% of the participants reported EGFR-TKI-induced skin toxicities; nearly 70% of these patients experienced xerosis and pruritus, while 50% had papulopustular eruptions and paronychia. Overall, the SRQOL was acceptable but varied

Table 2

Distribution of skin toxicity and skin-related quality of life in the study patients (N = 146).

Grade	Grade 1, 2, 3		Grade 0		Grade 1		Grade 2		Grade 3	
Symptoms	n	%	n	%	n	%	n	%	n	%
Xerosis	109	74.7	37	25.3	97	66.4	12.	8.2	0	0
Pruritus	104	71.2	42	28.8	89	61	13	8.9	2	1.4
Papulopustular	83	56.8	63	43.2	52	35.6	27	18.5	4	2.7
Paronychia	81	55.5	65	44.5	54	37	24	16.4	3	2.1
Locations vs symptoms			Xerosis*		Pruritus*		Papulopustular*		Paronychia*	
Scalp	48	32.9	39	81.3	39	81.3	42	87.6	-	-
Face	73	50	57	78.1	56	76.7	65	89.0	-	-
Trunk	53	36.3	49	92.5	50	94.3	29	54.7	-	-
Limbs	60	41.1	56	93.3	50	83.3	28	46.7	-	-
Fingers	81	55.5	59	72.8	58	71.6	58	71.6	81	100
Skin symptom impact (mean/SD)	5.38	2.65								
Skindex-16 (mean/SD)	13.96	16.55								

Skin symptom impact = symptom grade + number of locations.
* all grades.

Table 3

Relation among basic data, skin symptom impact and skin-related quality of life (N = 146).

	Skin symptom impact					Skin-related quality of life				
Variables	**r**	**Mean**	**SD**	**T**	***P***	**r**	**Mean**	**SD**	**t**	***P***
Age	−0.29				.000	−0.29				.000
Duration of treatment (d)	0.14				.09	−0.02				.84
Sex										
Male		5.57	2.36	0.64	.52		11.58	14.73	−1.28	.20
Female		5.27	2.79				15.24	17.39		
Marital status										
Married		5.48	2.84	0.27	.78		13.17	14.09	−0.35	.73
Unmarried		5.34	2.58				14.25	17.45		
Education										
High school and below		5.32	2.78	−0.41	.68		13.71	16.21	−0.27	.79
High school and above		5.51	2.34				14.51	17.48		
Smoking										
No		5.30	2.66	−0.52	.60		14.78	16.66	−0.52	.60
Yes		5.56	2.64				11.86	16.29		
Employed										
No		4.96	2.86	−1.92	.06		13.61	18.02	−0.25	.80
Yes		5.79	2.37				14.31	15.07		
Stage										
IIIB		5.07	2.28	−0.48	.63		10.56	16.30	−0.84	.40
IV		5.41	2.69				14.35	16.66		
ECOG										
0		5.35	2.57	−0.19	.85		14.16	16.17	0.24	.81
1/2/3		5.45	2.89				13.40	17.82		
EGFR-TKI										
Gefitinib		3.47	2.31	12.29	.000		6.96	14.80	3.98	.02
Erlotinib		5.84	2.49	(post-hoc test Afatinib > Gefitinib)			14.48	14.78	(post-hoc test Afatinib >Gefitinib)	
Afatinib		5.94	2.51				16.46	17.21		

ECOG PS = Eastern cooperative oncology group performance status, EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor, SD = standard deviation.

Table 4

Association between skin toxicity and skin-related quality of life (N = 146).

Variables		**Mean**	**SD**	***t***	***P***
Symptoms					
Xerosis	Yes	15.45	17.22	1.88	.062
	No	9.57	13.69		
Pruritus	Yes	15.75	17.42	2.08	.039
	No	9.52	13.37		
Papulopustular	Yes	20.39	18.73	6.66	.000
	No	5.48	5.96		
Paronychia	Yes	17.36	16.46	2.84	.005
	No	9.72	15.79		
Location					
Scalp	Yes	18.01	16.23	−2.09	.038
	No	11.97	16.43		
Face	Yes	19.12	17.52	−3.95	.000
	No	8.80	13.82		
Trunk	Yes	14.19	17.60	−0.13	.90
	No	13.83	16.02		
Limbs	Yes	12.10	15.18	1.14	.26
	No	15.26	17.42		
Fingers	Yes	17.36	16.46	−2.84	.005
	No	9.72	15.79		
Skin symptom impact					
	R = 0.50 *P* = .000				

SD = standard deviation.

Table 5

Association between skin toxicity and dose reduction (N = 146).

Variables		Reduced (n = 23)		Non-reduced (n = 123)			
Symptoms	**N**	**n**	**%**	**n**	**%**	χ^2	***P***
Xerosis (yes)	109	21	91.3	88	71.5	3.02	.08
Pruritus (yes)	104	20	87.0	84	68.3	2.45	.12
Papulopustular (yes)	83	17	73.9	66	53.7	2.47	.12
Paronychia (yes)	81	16	69.6	65	52.8	1.57	.21
Location							
Scalp (yes)	48	13	56.5	35	28.5	5.70	.02
Face (yes)	73	16	69.6	57	46.3	3.30	.07
Trunk (yes)	53	9	39.1	44	35.8	0.01	.94
Limbs (yes)	60	8	34.8	52	42.3	0.19	.66
Fingers (yes)	81	16	69.6	65	52.8	1.57	.21
		Mean	SD	Mean	SD	t	*P*
Skin symptom impact		7.35	1.89	5.01	2.61	−4.09	.000
Skin-related quality of life		26.22	23.51	11.67	13.87	−2.88	.008

greatly among the participants (ie, the SD was large). Patients who reported a greater impact on the skin experienced a worse quality of life. Specifically, younger patients and those treated with afatinib had higher SSI scores and a poorer quality of life. Moreover, the SSI score was associated with EGFR-TKI dose reduction.

The incidence rate of skin toxicity in our study was comparable to those reported previously.[4,5,9,10,17] Skin-related symptoms have generally been shown to appear immediately after the initiation of treatment and to persist for the entire treatment period.[6,16] Papulopustular eruptions are recognized as a clearly visible and less tolerable symptom because they usually appear on the scalp and face.[7] Their occurrence on the scalp results in hair having to be shaved off, which interferes with social activities and causes emotional distress. While paronychia is a painful condition of the nails, skin dryness and itching are unpleasant symptoms that cause emotional distress and affect daily life. Even though EGFR-TKI therapy can improve the survival of patients with advanced lung cancer, the resulting skin toxicity affects their quality of life,[5,9] and the goal of managing EGFR-TKI-associated skin toxicity is to minimize its impact on the quality of life.[13] Therefore, skin toxicity symptoms and their severities must be evaluated during routine assessments. Appropriate care guidelines should be incorporated into the clinical care plan to ensure the consistency of care among clinical staff and to serve as a basis for patient self-care.[17]

We found that younger patients tended to have a higher SSI score and poorer quality of life, which was consistent with data from a previous study that found that patients with lung cancer ≤50 years of age who underwent EGFR-TKI treatment experienced a lower quality of life than those >50 years.[9] Skin symptoms interfere with body image and social interactions, which results in additional emotional distress in young patients given that they are more socially active.[18]

Skin-related toxicities led to EGFR-TKI dose reductions during the 3-month treatment period. Patients who required dose reductions had been more severely impacted by skin-related symptoms than had those who did not require such dose reductions. The severity of skin reactions has been shown to have a significant positive correlation with EGFR-TKI dosage,[10] as dosage adjustment is one of interventions applied when skin symptoms are severe. Boone et al. noted that 30% of the patients in their study required EGFR-TKI dose delays or discontinuation owing to skin toxicity,[19] while Takeda et al. reviewed 21 studies and found skin toxicity to be one of the reasons that targeted therapy was terminated.[20] Notably, neither skin symptoms nor locations alone caused dose reductions in our study; rather, both factors combined were associated with dose reduction. To avoid having to reduce the dose, it is important to provide adequate information and instruct the patients to report symptoms as soon as they manifest.[21] To that end, the SSI scores in this study can be used to assess the degree of impact of the skin symptoms.

Our study had some limitations. Its cross-sectional nature made it difficult to detect the changing patterns of skin symptoms. Future studies that use a longitudinal design are required to ascertain the trajectory of the symptoms. Moreover, only four

Table 6

Skin symptom impact and dose reduction in different type of EGFR-TKI (N = 146).

		Skin symptom impact				Quality of life			
EFGR	**Dose**	**Mean**	**SD**	***t***	***P***	**Mean**	**SD**	***t***	***p***
Afatinib	Reduced	7.61	1.72	−3.39	.001*	28.87	22.97	−2.79	.01*
	Non-reduced	5.48	2.50			13.02	13.57		
Erlotinib	Reduced	6.67	3.21	−0.59	.55	23.26	33.09	−0.51	.66
	Non-reduced	5.75	2.45			13.54	12.34		
Gefitinib	Reduced	6.00	1.41	−1.64	.11	6.77	9.57	0.02	.98
	Non-reduced	3.33	2.27			6.97	15.20		

EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor, SD = standard deviation.
* $P < .05$.

symptoms were assessed in this study, although these are reportedly the most obvious and noteworthy skin-related symptoms in patients with NSCLC. Lastly, the prevalence of other skin reactions such as hair disturbances ought to be further examined in future studies.

5. Conclusions

Our results demonstrated that skin toxicity has significant effects on the quality of life of patients with advanced NSCLC who receive EGFR-TKIs as first-line therapy. Healthcare professionals should educate their patients regarding skin care following treatment with EGFR-TKIs. Additionally, skin assessment and individually tailored management should be regularly provided during the treatment period.

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References

[1] Ministry of Health and Welfare. (2019). 2019 Annual Report of Major Cause of Death. Available at: https://www.mohw.gov.tw/cp-16-48057-1.html. Accessed July 1, 2019.
[2] Fan H, Shao ZY, Xiao YY, et al. Incidence and survival of non-small cell lung cancer in Shanghai: a population-based cohort study. BMJ Open 2015;5:e009419.
[3] Polanski J, Jankowska-Polanska B, Rosinczuk J, et al. Quality of life of patients with lung cancer. Onco Targets Ther 2016;9:1023–8.
[4] Ding PN, Lord SJ, Gebski V, et al. Risk of treatment-related toxicities from EGFR tyrosine kinase inhibitors: a meta-analysis of clinical trials of gefitinib, erlotinib, and afatinib in advanced EGFR-mutated non-small cell lung cancer. J Thorac Oncol 2016;12:633–43.
[5] Normando SR, Cruz FM, Del Giglio A. Cumulative meta-analysis of epidermal growth factor receptor-tyrosine kinase inhibitors as first-line therapy in metastatic non-small-cell lung cancer. Anticancer Drugs 2015;26:995–1003.
[6] Zhang Y, Sheng J, Yang Y, et al. Optimized selection of three major EGFR-TKIs in advanced EGFR-positive non-small cell lung cancer: a network meta analysis. Oncotarget 2016;7:20093–108.
[7] Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer 2006;6:803–12.
[8] Kozuki T. Skin problems and EGFR-tyrosine kinase inhibitor. Jpn J Clin Oncol 2016;46:291–8.
[9] Joshi SS, Ortiz S, Witherspoon JN, et al. Effects of epidermal growth factor receptor inhibitor-induced dermatologic toxicities on quality of life. Cancer 2010;9:3916–23.
[10] Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol 2010;28:1351–7.
[11] Tischer B, Bilang M, Kraemer M, et al. A survey of patient and physician acceptance of skin toxicities from anti-epidermal growth factor receptor therapies. Support Care Cancer 2018;26:1169–79.
[12] Masago K, Imamichi F, Masuda Y, et al. Team management of skin rash associated with use of epidermal growth factor receptor-tyrosine kinase inhibitors. Asia Pac J Oncol Nurs 2018;5:430–4.
[13] Li T, Perez-Soler R. Skin toxicities associated with epidermal growth factor receptor inhibitors. Target Oncol 2009;4:107–19.
[14] Chren MM. The Skindex instruments to measure the effects of skin disease on quality of life. Dermatol Clin 2012;30:231–6.
[15] He Z, Lu C, Chren MM, et al. Development and psychometric validation of the Chinese version of Skindex-29 and Skindex-16. Health Qual Life Outcomes 2014;12:190.
[16] Osio A, Mateus C, Soria JC, et al. Cutaneous side-effects in patients on long-term treatment with epidermal growth factor receptor inhibitors. Br J Dermatol 2009;161:515–21.
[17] Chu CY, Chen KY, Chang WC, et al. Taiwanese dermatological association consensus for the prevention and management of epidermal growth factor receptor tyrosine kinase inhibitor-related skin toxicities. J Formos Med Assoc 2017;116:413–23.
[18] Esser P, Mehnert A, Johansen C, et al. Body image mediates the effect of cancer-related stigmatization on depression: a new target for intervention. Psychooncology 2017;27:193–8.
[19] Boone SL, Rademarker A, Liu D, et al. Impact and management of skin toxicity associated with anti-epidermal growth factor receptor therapy: survey results. Oncology 2007;72:152–9.
[20] Takeda M, Okamoto I, Nakagawa K. Pooled safety analysis of EGFR-TKI treatment for EGFR mutation-positive non-small cell lung cancer. Lung Cancer 2015;88:74–9.
[21] Melosky B, Leighl NB, Rothenstein J, et al. Management of EGFR TKI-induced dermatologic adverse events. Curr Oncol 2015;22:123–32.