Scientific Research Publishing

Open Journal of Nursing, 2019, 9, 1226-1239
https://www.scirp.org/journal/ojn
ISSN Online: 2162-5344
ISSN Print: 2162-5336

Association between Subjective Evaluation of Skin Toxicities and Quality of Life in Patients with Lung Cancer Undergoing Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor Treatment: A Pilot Study for Developing Skin Toxicity Assessment

Kengo Hirayama[1], Ya Su[2], Yasuyuki Ikezawa[3], Megumi Chiba[3], Kenichiro Ito[4], Michiko Yuki[1]

[1]Faculty of Health Sciences, Hokkaido University, Sapporo, Japan
[2]Graduate School of Health Sciences, Hokkaido University, Sapporo, Japan
[3]Department of Respiratory Medicine, Oji General Hospital, Tomakomai, Japan
[4]KKR Sapporo Medical Center, Sapporo, Japan
Email: khirayama@hs.hokudai.ac.jp

How to cite this paper: Hirayama, K., Su, Y., Ikezawa, Y., Chiba, M., Ito, K. and Yuki, M. (2019) Association between Subjective Evaluation of Skin Toxicities and Quality of Life in Patients with Lung Cancer Undergoing Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor Treatment: A Pilot Study for Developing Skin Toxicity Assessment. *Open Journal of Nursing*, **9**, 1226-1239.
https://doi.org/10.4236/ojn.2019.912089

Received: November 11, 2019
Accepted: December 15, 2019
Published: December 18, 2019

Abstract

Purposes: Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) exert satisfactory therapeutic effects in lung cancer patients. However, the resultant skin toxicity can deteriorate patients' quality of life (QoL). Differences exist in skin toxicity evaluation between patients and clinicians. We aimed to clarify the association between the subjective evaluation of skin toxicities and QoL in lung cancer patients and to establish a document of scale development in the subjective evaluation of skin toxicity. **Methods**: We used self-administered questionnaires to evaluate 12 lung cancer patients receiving EGFR-TKI treatment. Indices of QoL were generated using the Functional Assessment of Cancer Therapy-Lung and Hospital Anxiety and Depression Scale, and a subjective evaluation questionnaire concerning skin toxicity was completed. The data were collected immediately before treatment initiation and at 4 weeks post treatment. **Results**: In the subjective evaluation of skin toxicity, four patients (33.3%) were classified as ≥Grade 2 (painful group), experiencing painful pruritus at the emergence site of the skin rash or xerosis. In this group, the QoL scores of physical and emotional aspects declined after treatment. Conversely, patients in the painless group (Grade 0 - 1) demonstrated an improved emotional QoL following treatment (p = 0.028). **Conclusions**: Lung cancer patients suffering from painful skin toxici-

ty tended to show a decline in the physical and emotional aspects of QoL following EGFR-TKI treatment. The skin toxicity questionnaire was useful from the point of view of a subjective evaluation and could be a powerful assessment tool in future clinical settings with further modification.

Keywords

Lung Cancer, EGFR-Tyrosine Kinase Inhibitors, Skin Toxicity, Quality of Life

1. Introduction

Lung cancer has an extremely poor prognosis among malignant tumors. According to the World Health Organization, it was the sixth-leading cause of mortality in 2016, responsible for 1.7 million deaths worldwide [1]. This mortality rate was the highest among all malignancies [2]. Lung cancer morbidity increases with age, and the median age at diagnosis is 70 years [3]. Thus, it is predicted that the proportion of elderly people with lung cancer will increase globally due to the increasing aging population.

Following lung cancer diagnosis, many patients choose to undergo chemotherapy. In recent years, the development of chemotherapeutic drugs has become highly advanced, and since the 2000s, the use of molecular targeted agents has become established in the treatment of non-small cell lung cancer (NSCLC) via gene alternations, such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase, a receptor tyrosine kinase. Previous clinical studies have demonstrated the efficacy of EGFR-tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib, erlotinib, afatinib, and osimertinib, as first-line chemotherapeutics for patients with EGFR-mutated NSCLC [4] [5] [6], with some reports showing efficacy in elderly patients [7] [8]. Unfortunately, skin toxicity is the most common adverse effect of EGFR-TKIs, occurring in >80% of patients [9]. Furthermore, several studies have identified correlations between the incidence and severity of skin toxicities and overall survival (OS) [10] [11] [12]. Hence, the continuation of EGFR-TKI involves coping with the resultant skin toxicity via appropriate skin care measures to prevent deterioration.

In this respect, the aim is not only to support the treatment side effect but also to maintain the patient's daily quality of life (QoL) because the EGFR-TKI treatment prolongs their life. In some QoL studies of lung cancer patients undergoing treatment with molecular targeted agents, a higher OS, progression-free survival, and QoL has been reported in those receiving treatment with EGFR-TKIs compared with those treated with cytotoxic chemotherapy [13] [14] [15] [16] [17]. Contrary to the therapeutic effect, it has become evident that the emergence of skin toxicity caused by EGFR-TKIs affects the daily life of patients, leading to a decreased QoL [18] [19] [20]. To evaluate the adverse events of chemotherapy, the National Cancer Institute established the Common Terminology Criteria for Adverse Events (CTCAE) as an international standard, in-

cluding skin toxicities [21]. However, the CTCAE is not a useful subjective assessment tool for skin toxicities. Novello *et al*. (2014) argues that there are differences between patients and clinicians in the evaluation of the skin toxicity of molecular targeted therapies, with clinicians underestimating the severity of the situation [22]. Additionally, it has been suggested that severe symptoms of skin toxicity greatly influence the psychological state of the patient [23]. To obtain more insight into how skin toxicity affects the patient's QoL, the association between the subjective evaluation of skin toxicity and QoL requires elucidation.

Therefore, our study aims to clarify the association between the subjective evaluation of skin toxicity and QoL in lung cancer patients receiving EGFR-TKIs. These results could be used as a document of scale development in the subjective evaluation of skin toxicity.

2. Methods

2.1. Study Design and Participants

We conducted this prospective observational study between September 2017 and January 2019 at two hospitals in Hokkaido, Japan. All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethics committee of the Faculty of Health Sciences, Hokkaido University (Ethics Code: 16-52-1), Oji General Hospital (Ethics Code: OGH2017-15), and KKR Sapporo Medical Center (Ethics Code: 29-6) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study. Fourteen patients satisfied the following inclusion criteria: 1) diagnosed with advanced or recurrent NSCLC, 2) diagnosed as EGFR mutation-positive, 3) about to begin treatment with single-agent EGFR-TKI, 4) demonstrating no obvious skin disease or skin toxicity at the beginning of treatment considered to affect this study, 5) having cognitive functions capable of communicating in Japanese, and 6) able to provide consent following an explanation of the research. Patients were not allowed to enroll in this study in the event of the following: 1) not notified of lung cancer diagnosis, 2) Eastern Cooperative Oncology Group (ECOG) performance status ≥ 3. Patients were introduced to the study by their doctor.

2.2. Data Sources

Data collection included the patient's attributes (sex, age, marital status, employment status, and smoking history) from the medical records, the medical condition (disease stage, treatment history, ECOG performance status [PS], and therapeutic agent) and patient-reported outcomes. Self-administered questionnaires were used to investigate patient-reported outcomes. The initial evaluation prior to the commencement of EGFR-TKIs (T0) was conducted at the hospital following admission. Because skin toxicity characteristically manifests within the

first 1 - 3 weeks of treatment [24], the post-treatment evaluation occurred 4 weeks after treatment (T1) by mailing a questionnaire to the patient's home. A subjective evaluation of skin toxicity was added to the items at T0 for the evaluation at T1.

2.3. Outcome Measures

2.3.1. Evaluation of Skin Toxicity

Since there was no established survey form to subjectively evaluate the skin toxicity caused by EGFR-TKI, we utilized a questionnaire at T1 that was created independently by researchers following CTCAE version 4.0. According to a previous study, pain and pruritus at the site of skin toxicities were reported as causes of patient distress [25], which negatively affected their QoL [26] [27]. Therefore, the contents of the questionnaire included an assessment of the degree of pain and pruritus at the symptom appearance site of skin rash, xerosis, and paronychia (**Table 1**). The skin toxicity severity was classified as absent (Grade 0), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or very severe (Grade 4) according to the classification of CTCAE v4.0. [21].

2.3.2. QoL Evaluation

The health-related QoL of lung cancer patients was assessed using the Japanese version of Functional Assessment of Cancer Therapy (FACT)-Lung (FACT-L) version 4.0, a combination of the 27-item FACT-General (FACT-G) and the 9-item Lung Cancer Sub-scale (LCS) [28]. The FACT-G consists of physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB) sub-scale scores. A total FACT-L score of 0 - 136 is obtained by summing the FACT-G and LCS (two of the nine items are not scored). Each item is scored according to a 5-point Likert scale. Higher FACT-L scores correspond to a better QoL.

2.3.3. Emotional Problems

Psychological distress was measured using Hospital Anxiety and Depression Scale (HADS), consisting of 14 items measuring anxiety (HADS-A) and depression

Table 1. Subjective evaluation questionnaire of skin toxicity by EGFR-TKI for non-small cell lung cancer patients.

	Degree of Skin Toxicity	Grade 0 absent	Grade 1 mild	Grade 2 moderate	Grade 3 severe	Grade 4 very severe
1	Pain in the area where papules and/or pustules emerge (skin rash)	0	1	2	3	4
2	Pruritus in the area where papules and/or pustules emerge (skin rash)	0	1	2	3	4
3	Pain in the area where skin is dry (xerosis)	0	1	2	3	4
4	Pruritus in the area where skin is dry (xerosis)	0	1	2	3	4
5	Pain in the disruption part around the nail (paronychia)	0	1	2	3	4

(HADS-D). Each item is scored according to a 4-point Likert scale, and the total score range is 0 to 21, with 0 - 7 categorized as "no," 8 - 10 as "probable," and ≥ 11 as "present" anxiety or depression [29]. A higher score indicates higher anxiety and depression levels. We used the validated Japanese version of HADS [30].

2.4. Data Sources

The FACT-L and HADS scores were checked for normality using the Shapiro-Wilk test followed by the Wilcoxon signed rank test to evaluate the differences between the average values obtained at T0 and T1. The subjective evaluation of skin toxicity was classified into two severity groups (Grade 0-1 vs. ≥ Grade 2), and the association with QoL was also analyzed. As a severity classification of skin toxicities, Grade 0-1 was a group without distress regardless of the presence or absence of symptoms (painless group), and ≥Grade 2 was a group with distressful symptoms (painful group). Statistical analysis was conducted using SPSS Statistics version 22.0 (IBM Corp., Armonk, NY), and each level of significance was set at $p < 0.05$.

3. Results

3.1. Patients and Characteristics

Table 2 illustrates the demographic characteristics related to patient treatment. Of the 14 patients who fulfilled the eligibility criteria, 2 were excluded because PS decreased owing to disease progression and comorbidity, and a final cohort of 12 patients (85.7%) was analyzed. The average patient age was 65.8 years (standard deviation = 6.1). Nine patients (75.0%) were married, and three (25.0%) were employed. Almost all patients (83.3%) had advanced cancer stage 3 or 4. There were eight patients with no prior experience of receiving chemotherapy who were being treated for the first time. The treatment agents were gefitinib, erlotinib, afatinib, and osimertinib (1/1/7/3).

3.2. Subjective Evaluation of Skin Toxicity

The evaluation of skin toxicity at T1 by the study subjects was investigated using a questionnaire asking about pain and pruritus in the areas where a skin rash or xerosis appeared and pain due to paronychia (Table 3). The severity of skin toxicity (Grade 0 - Grade 4) was based on CTCAE version 4.0. At T1, 4/12 patients (33.3%) experienced a skin toxicity ≥ Grade 2, and many patients were particularly aware of pruritus associated with skin rash or xerosis. On the other hand, no pain was associated with xerosis ≥ Grade 2. Two patients reported no skin toxicity (Grade 0), and six evaluated skin toxicity as Grade 1.

3.3. QoL in Lung Cancer Patients

3.3.1. Association of Skin Toxicity with FACT-L

The self-administered FACT-L questionnaires were completed just before treatment commenced and at one month after treatment (Table 4). There was no significant difference in the FACT-L score for all patients from T0 to T1 (93.6

Table 2. Demographic and disease related characteristics.

	N (%) or M ± SD	
Characteristics	Male (*N* = 6)	Female (*N* = 6)
Age	66.2 ± 7.1	65.5 ± 5.7
Elderly (≥65 years)	4 (66.7) 69.5 ± 5.9	5 (83.3) 67.2 ± 4.4
Not Elderly (<65 years)	2 (33.3) 59.5 ± 3.5	1 (16.7) 57.0 ± 0.0
Employed		
Yes	2 (33.3)	1 (16.7)
No	4 (66.7)	5 (83.3)
Married		
Yes	4 (66.7)	5 (83.3)
No	2 (33.3)	1 (16.7)
Smoking history		
Yes	6 (100.0)	2 (33.3)
No	0 (0.0)	4 (66.7)
Diagnosis Stage		
Postoperative Recurrence	1 (16.7)	1 (16.7)
III	1 (16.7)	0 (0.0)
IV	4 (66.7)	5 (83.3)
Surgery history		
Yes	2 (33.3)	1 (16.7)
No	4 (66.7)	5 (83.3)
Chemotherapy history		
Yes	2 (33.3)	2 (33.3)
No	4 (66.7)	4 (66.7)
ECOG Performance Status		
0 (Baseline/4 weeks follow-up)	3 (50.0)/0 (0.0)	3 (50.0)/2 (33.3)
1 (Baseline/4 weeks follow-up)	2 (33.3)/4 (66.7)	3 (50.0)/2 (33.3)
≥2 (Baseline/4 weeks follow-up)	1 (16.7)/2 (33.3)	0 (0.0)/2 (33.3)
EGFR Inhibitors		
Gefitinib	1 (16.7)	0 (0.0)
Erlotinib	0 (0.0)	1 (16.7)
Afatinib	5 (83.3)	2 (33.3)
Osimertinib	0 (0.0)	3 (50.0)

Abbreviation: SD, Standard Deviation; ECOG, Eastern Cooperative Oncology Group; EGFR, Epidermal Growth Factor Receptor.

± 17.6 vs. 94.2 ± 19.3), and no significant score change was observed for the PWB, SWB, EWB, FWB, and LCS subscales. The QoL change from T0-T1 in the painless group (Grade 0-1) revealed a significant difference in EWB ($p = 0.028$). There was also an improvement in the total score, PWB, and LCS in the painless group, but no significant differences were observed. In the painful group

Table 3. Subjective evaluation of skin toxicity in the grade classification.

Skin Toxicity	*N* = 12 (%)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin Rash					
pain	8 (66.7)	2 (16.7)	1 (8.3)	1 (8.3)	0 (0.0)
pruritus	6 (50.0)	3 (25.0)	1 (8.3)	2 (16.7)	0 (0.0)
Xerosis					
pain	7 (58.3)	5 (41.7)	0 (0.0)	0 (0.0)	0 (0.0)
pruritus	6 (50.0)	4 (33.3)	1 (8.3)	1 (8.3)	0 (0.0)
Paronychia					
pain	7 (58.3)	4 (33.3)	0 (0.0)	1 (8.3)	0 (0.0)

Table 4. Association of skin toxicity with FACT-L before and post treatment.

	All *N* = 12			Skin Toxicity (Grade 0-1) *N* = 8			Skin Toxicity (Grade ≥ 2) *N* = 4		
	Mean ± SD			Mean ± SD			Mean ± SD		
Construct (score range)	Baseline	4 weeks follow-up	*p*-value	Baseline	4 weeks follow-up	*p*-value	Baseline	4 weeks follow-up	*p*-value
FACT-L									
Total (0 - 136)	93.57 ± 17.59	94.20 ± 19.28	0.638	93.50 ± 20.03	96.86 ± 20.20	0.263	93.71 ± 14.07	88.88 ± 18.83	0.465
PWB (0 - 28)	22.58 ± 6.14	22.17 ± 5.02	0.875	22.00 ± 5.63	23.13 ± 5.08	0.438	23.75 ± 7.85	20.25 ± 4.99	0.269
SWB (0 - 28)	17.74 ± 7.79	16.95 ± 9.36	0.386	19.88 ± 7.38	18.61 ± 9.32	0.397	13.46 ± 7.66	13.63 ± 9.81	1.000
EWB (0 - 24)	17.58 ± 4.94	17.92 ± 5.70	0.663	15.88 ± 4.02	18.13 ± 5.69	0.028*	21.00 ± 5.35	17.50 ± 6.56	0.066
FWB (0 - 28)	16.25 ± 6.12	16.58 ± 7.96	0.724	17.00 ± 7.21	16.63 ± 8.35	1.000	14.75 ± 3.40	16.50 ± 8.35	0.715
LCS (0 - 28)	19.42 ± 4.10	20.58 ± 4.32	0.422	18.75 ± 4.43	20.38 ± 4.03	0.235	20.75 ± 3.50	21.00 ± 5.48	0.715

Abbreviations: FACT-L, Functional Assessment of Cancer Therapy-Lung. *$p < 0.05$.

(≥Grade 2), although there were no significant differences in all items from T0 - T1, the EWB tended to decrease ($p = 0.066$). Furthermore, although there was no significant difference in total and PWB scores, the decreased results contrasted with those of the painless group.

3.3.2. Association of Skin Toxicity with HADS

In all patients, the HADS-A and HADS-D scores were not significantly different between T0 and T1 (Table 5). Additionally, all scores were < 8, falling within the normal range. For both the painful and painless skin toxicity groups, there were no significant difference between the scores of HADS-A and HADS-D at T0 and T1. In the painless group (Grade 0-1), the mean scores of both anxiety and depression were decreased. Moreover, as Figure 1 shows, since the total HADS score decreased except for one patient, it follows that patients without pain suffering from skin toxicity experienced little distress after treatment commencement, with the HADS-D scale showing an improvement ($p = 0.089$). However,

Table 5. Association of skin toxicity with HADS before and post treatment.

	All N = 12			Skin Toxicity (Grade 0-1) N = 8			Skin Toxicity (Grade ≥ 2) N = 4		
	Mean ± SD			Mean ± SD			Mean ± SD		
Construct (score range)	Baseline	4 weeks follow-up	*p*-value	Baseline	4 weeks follow-up	*p*-value	Baseline	4 weeks follow-up	*p*-value
HADS									
[a]HADS-A (0 - 21)	5.33 ± 3.45	5.25 ± 4.05	0.964	5.88 ± 1.96	5.13 ± 3.44	0.551	4.25 ± 5.68	5.50 ± 5.69	0.257
[b]HADS-D (0 - 21)	6.58 ± 4.60	6.58 ± 5.50	0.574	7.25 ± 3.92	5.25 ± 4.40	0.089	5.25 ± 6.19	9.25 ± 7.18	0.285

[a]HADS-A: Defined as a score of ≥ 8 for the scale of anxiety. [b]HADS-D: Defined as a score of ≥ 8 for the subscale depression. Abbreviations: HADS, Hospital Anxiety and Depression Scale.

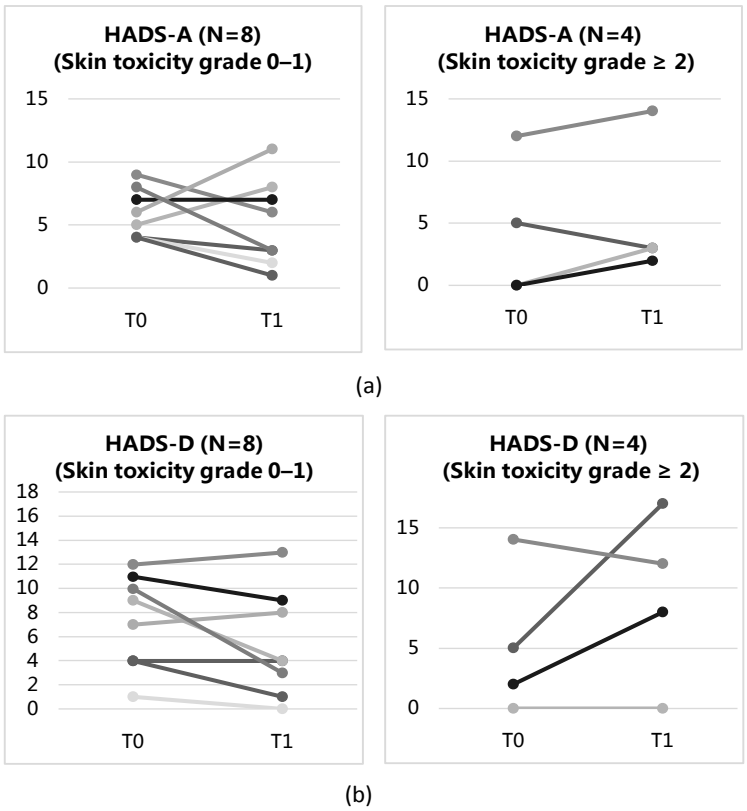

Figure 1. Trends of HADS score change according to the degree of skin toxicity from T0 to T1 (Grade 0-1 vs Grade 2 ≥): a anxiety and b depression scores.

in the painful group, the mean HADS-A and HADS-D scores were increased, indicating a distressed condition after the treatment had commenced. The HADS-D score was 9.3 ± 7.2 at T1, indicating that patients with pain suffering from skin toxicity tended to be depressed.

4. Discussion

Our study results revealed the subjective evaluation of the skin toxicity experienced by lung cancer patients undergoing treatment with EGFR-TKIs and the

association with QoL before and after treatment. There was only one patient with a PS < 2 at T0, but this increased to four following treatment initiation; therefore, it is thought that adverse events, including skin toxicities and disease progression were contributing factors. Additionally, most patients who suffered pain from skin toxicity and disease progression were evaluated for pruritus at the sites where skin rash and xerosis appeared. A previous study has shown that a strong degree of pruritus affects a patient's QoL [27]. Because pruritus and pain are easily recognizable symptoms, it is important to evaluate them both objectively and subjectively.

Regarding FACT-L, there were no significant change in the score of both total and subscale items at T0 and T1 when the study subjects were assessed as a single group. In a QoL survey of 30 patients with lung cancer in Brazil [31], the total FACT-L score during the non-treatment period was 98.9, which was similar to the score of our study subjects. There were no significant differences between the patients in the painful group; however, the total and PWB scores decreased between T0 and T1. In particular, since the EWB QoL subscale tended to deteriorate, this suggests that physical and psychological suffering is experienced due to skin toxicity. On the other hand, patients in the painless group demonstrated increased PWB and LCS scores after treatment, and the EWB showed a significant improvement. Therefore, we consider that the therapeutic effect of EGFR-TKIs contributed to an improvement in the symptoms accompanying lung cancer, such as dyspnea and coughing. Furthermore, we suggest that improvements in pain symptoms and awareness of the mild suppression of adverse events lead to an increased EWB score. Having considered these matters, for the continuation of EGFR-TKI treatment, it is important to relieve physical pain by practicing skin management to the extent that the pain of skin toxicity is not felt because this is liable to cause deterioration of the physical and emotional QoL.

Regarding HADS in the painful group, both HADS-A and HADS-D scores worsened after treatment, and it was considered that pain caused by skin toxicity was a contributing factor. Similar results were reflected in the EWB of FACT-L. Yanwei *et al.* [32] reported that lung cancer patients who were receiving erlotinib and aware of their diagnosis and prognosis showed an improved HADS score following treatment. Considering this, a reduction in psychological burden is expected by sharing information on the relationship between skin toxicity and the therapeutic effect with those patients who experience pain caused by treatment toxicity. Additionally, the decline in PS due to age and treatment effects has been reported as a risk factor affecting the psychological aspect of lung cancer patients [33]. In this survey, there were many elderly patients, and most of them experienced deterioration in PS following treatment. Because PS deterioration leads to a decreased QoL in the elderly [34], it is considered that the suppression of adverse events as much as possible, including skin toxicity, is necessary for treatment continuation and to maintain PS.

Thus, our analysis based on the subjective evaluation of skin toxicity revealed in part the association between skin toxicity and QoL. To maintain the QoL of

lung cancer patients receiving EGFR-TKIs, it is important to sustain the pain caused by skin toxicity at an acceptable level. To that end, it is necessary to perform an assessment using questionnaires that subjectively evaluate skin toxicities. A further study to refine the composition of the subjective evaluation questionnaire on skin toxicity should be conducted.

5. Implication for Nursing Practice

From the results of this study, patients with skin toxicities tended to have lower physical and emotional QoL than patients without pain. In particular, it was the pruritus at the site of the appearance of skin rash and xerosis that was cited as a contributing factor to the pain for the patients with skin toxicities. In this respect, it is critical that oncology nurses to sufficiently assess the subjective evaluation in addition to the objective evaluation for the skin toxicity caused by EGFR-TKI. Furthermore, it is important that they are involved in improving physical QoL of patients by performing appropriate management practices to control symptoms such as pain and pruritus, which may lead to an eventual improvement in the emotional QoL of patients. In addition, as most elderly patients in this study had a decrease in PS after beginning the treatment, it may be necessary to manage adverse events, including skin toxicities, to prevent PS deterioration in order to maintain QoL and continue the treatment.

6. Limitations of the Study

It is difficult to define the conclusions of this study because the number of subjects is small, which may lower its statistical power. Moreover, no control group was included. In future, the number of subjects should be increased to improve the reliability of the results. Furthermore, in addition to both a subjective assessment and objective evaluation of skin toxicity, the accuracy of the evaluation requires improvement. Finally, it is possible that adverse events other than skin toxicities can also affect patient QoL.

7. Conclusion

Lung cancer patients undergoing treatment with EGFR-TKIs showed a tendency toward a lower QoL in physical and emotional aspects owing to the presence of painful skin toxicities. An improvement in the emotional aspect of QoL was recognized by suppressing the symptoms of skin toxicity to an acceptable level. Consequently, it can be presumed that by maintaining a condition judged as mild in the subjective evaluation of skin toxicity, a decreased QoL could be prevented. Therefore, the skin toxicity questionnaire was important from the point of view of a subjective evaluation, and it can be useful tool as an appropriate assessment of skin toxicities in clinical settings.

Acknowledgements

This work was supported by the JSPS KAKENHI (Grant Number JP 16H06605).

The authors would like to thank Enago (www.enago.jp) for the English language review.

Conflicts of Interest

All authors have read and approved the manuscript and have no conflicts of interest to declare.

References

[1] World Health Organization (2018) The Top 10 Causes of Death. https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death

[2] Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D. and Bray, F. (2015) Cancer Incidence and Mortality Worldwide: Sources, Methods and Major Patterns in GLOBOCAN 2012. *International Journal of Cancer*, **136**, E359-E386. https://doi.org/10.1002/ijc.29210

[3] Miller, K.D., Siegel, R.L., Lin, C.C., Mariotto, A.B., Kramer, J.L., Rowland, J.H., Stein, K.D., Alteri, R. and Jemal, A. (2016) Cancer Treatment and Survivorship Statistics, 2016. *CA*: *A Cancer Journal for Clinicians*, **66**, 271-289. https://doi.org/10.3322/caac.21349

[4] Mitsudomi, T., Morita, S., Yatabe, Y., Negoro, S., Okamoto, I., Tsurutani, J., Seto, T., Satouchi, M., Tada, H., Hirashima, T., Asami, K., Katakami, N., Takada, M., Yoshioka, H., Shibata, K., Kudoh, S., Shimizu, E., Saito, H., Toyooka, S., Nakagawa, K. and Fukuoka, M. (2010) Gefitinib versus Cisplatin Plus Docetaxel in Patients with Non-Small-Cell Lung Cancer Harbouring Mutations of the Epidermal Growth Factor Receptor (WJTOG3405): An Open Label, Randomised Phase 3 Trial. *The Lancet Oncology*, **11**, 121-128. https://doi.org/10.1016/S1470-2045(09)70364-X

[5] Zhou, C., Wu, Y.L., Chen, G., Feng, J., Liu, X.Q., Wang, C., Zhang, S., Wang, J., Zhou, S., Ren, S., Lu, S., Zhang, L., Hu, C., Hu, C., Luo, Y., Chen, L., Ye, M., Huang, J., Zhi, X., Zhang, Y., Xiu, Q., Ma, J., Zhang, L. and You, C. (2015) Final Overall Survival Results from a Randomised, Phase III Study of Erlotinib versus Chemotherapy as First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer (OPTIMAL, CTONG-0802). *Annals of Oncology*, **26**, 1877-1883. https://doi.org/10.1093/annonc/mdv276

[6] Yang, J.C., Wu, Y.L., Schuler, M., Sebastian, M., Popat, S., Yamamoto, N., Zhou, C., Hu, C.P., O'Byrne, K., Feng, J., Lu, S., Huang, Y., Geater, S.L., Lee, K.Y., Tsai, C.M., Gorbunova, V., Hirsh, V., Bennouna, J., Orlov, S., Mok, T., Boyer, M., Su, W.C., Lee, K.H., Kato, T., Massey, D., Shahidi, M., Zazulina, V. and Sequist, L.V. (2015) Afatinib versus Cisplatin-Based Chemotherapy for EGFR Mutation-Positive Lung Adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): Analysis of Overall Survival Data from Two Randomised, Phase 3 Trials. *The Lancet Oncology*, **16**, 141-151. https://doi.org/10.1016/S1470-2045(14)71173-8

[7] Inoue, Y., Inui, N., Asada, K., Karayama, M., Matsuda, H., Yokomura, K., Koshimizu, N., Imokawa, S., Yamada, T., Shirai, T., Kasamatsu, N. and Suda, T. (2015) Phase II Study of Erlotinib in Elderly Patients with Non-Small Cell Lung Cancer Harboring Epidermal Growth Factor Receptor Mutations. *Cancer Chemotherapy and Pharmacology*, **76**, 155-161. https://doi.org/10.1007/s00280-015-2784-x

[8] Rossi, S., D'Argento, E., Schinzari, G., Dadduzio, V., Di Noia, V., Cassano, A. and Barone, C. (2016) Are TKIs Favourable for the Elderly with Non-Small-Cell Lung Cancer? *Oncotarget*, **7**, 46871-46877. https://doi.org/10.18632/oncotarget.9389

[9] Peuvrel, L., Bachmeyer, C., Reguiai, Z., Bachet, J.B., André, T., Bensadoun, R.J.,

Bouché, O., Ychou, M. and Dréno, B. (2012) Semiology of Skin Toxicity Associated with Epidermal Growth Factor Receptor (EGFR) Inhibitors. *Supportive Care in Cancer*, **20**, 909-921. https://doi.org/10.1007/s00520-012-1404-0

[10] Wacker, B., Nagrani, T., Weinberg, J., Witt, K., Clark, G. and Cagnoni, P.J. (2007) Correlation between Development of Rash and Efficacy in Patients Treated with the Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Erlotinib in Two Large Phase III Studies. *Clinical Cancer Research*, **13**, 3913-3921. https://doi.org/10.1158/1078-0432.CCR-06-2610

[11] Bonner, J.A., Harari, P.M., Giralt, J., Cohen, R.B., Jones, C.U., Sur, R.K., Raben, D., Baselga, J., Spencer, S.A., Zhu, J., Youssoufian, H., Rowinsky, E.K. and Ang, K.K. (2010) Radiotherapy Plus Cetuximab for Locoregionally Advanced Head and Neck Cancer: 5-Year Survival Data from a Phase 3 Randomised Trial, and Relation between Cetuximab-Induced Rash and Survival. *The Lancet Oncology*, **11**, 21-28. https://doi.org/10.1016/S1470-2045(09)70311-0

[12] Peeters, M., Siena, S., Van Cutsem, E., Sobrero, A., Hendlisz, A., Cascinu, S., Kalofonos, H., Devercelli, G., Wolf, M. and Amado, R.G. (2009) Association of Progression-Free Survival, Overall Survival, and Patient-Reported Outcomes by Skin Toxicity and KRAS Status in Patients Receiving Panitumumab Monotherapy. *Cancer*, **115**, 1544-1554. https://doi.org/10.1002/cncr.24088

[13] Yang, Y.P., Ma, Y.X., Huang, Y., Zhao, Y.Y., Fang, W.F., Hong, S.D., Tian, Y., Xue, C., Sheng, J. and Zhang, L. (2015) QoL Analyses from INFORM Study, a Phase III Study of Gefitinib versus Placebo as Maintenance Therapy in Advanced NSCLC. *Scientific Reports*, **5**, 11934. https://doi.org/10.1038/srep11934

[14] Han, J.Y., Park, K., Kim, S.W., Lee, D.H., Kim, H.Y., Kim, H.T., Ahn, M.J., Yun, T., Ahn, J.S., Suh, C., Lee, J.S., Yoon, S.J., Han, J.H., Lee, J.W., Jo, S.J. and Lee, J.S. (2012) First-SIGNAL: First-Line Single-Agent Iressa versus Gemcitabine and Cisplatin Trial in Never-Smokers with Adenocarcinoma of the Lung. *Journal of Clinical Oncology*, **30**, 1122-1128. https://doi.org/10.1200/JCO.2011.36.8456

[15] Oizumi, S., Kobayashi, K., Inoue, A., Maemondo, M., Sugawara, S., Yoshizawa, H., Isobe, H., Harada, M., Kinoshita, I., Okinaga, S., Kato, T., Harada, T., Gemma, A., Saijo, Y., Yokomizo, Y., Morita, S., Hagiwara, K. and Nukiwa, T. (2012) Quality of Life with Gefitinib in Patients with EGFR-Mutated Non-Small Cell Lung Cancer: Quality of Life Analysis of North East Japan Study Group 002 Trial. *The Oncologist*, **17**, 863-870. https://doi.org/10.1634/theoncologist.2011-0426

[16] Mok, T.S., Wu, Y.L., Thongprasert, S., Yang, C.H., Chu, D.T., Saijo, N., Sunpaweravong, P., Han, B., Margono, B., Ichinose, Y., Nishiwaki, Y., Ohe, Y., Yang, J.J., Chewaskulyong, B., Jiang, H., Duffield, E.L., Watkins, C.L., Armour, A.A. and Fukuoka, M. (2009) Gefitinib or Carboplatin-Paclitaxel in Pulmonary Adenocarcinoma. *The New England Journal of Medicine*, **361**, 947-957. https://doi.org/10.1056/NEJMoa0810699

[17] Zhou, C., Wu, Y.L., Chen, G., Feng, J., Liu, X.Q., Wang, C., Zhang, S., Wang, J., Zhou, S., Ren, S., Lu, S., Zhang, L., Hu, C., Hu, C., Luo, Y., Chen, L., Ye, M., Huang, J., Zhi, X., Zhang, Y., Xiu, Q., Ma, J., Zhang, L. and You, C. (2011) Erlotinib versus Chemotherapy as First-Line Treatment for Patients with Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer (OPTIMAL, CTONG-0802): A Multicentre, Open-Label, Randomised, Phase 3 Study. *The Lancet Oncology*, **12**, 735-742. https://doi.org/10.1016/S1470-2045(11)70184-X

[18] Wagner, L.I. and Lacouture, M.E. (2007) Dermatologic Toxicities Associated with EGFR Inhibitors: The Clinical Psychologis's Perspective. Impact on Health-Related Quality of Life and Implications for Clinical Management of Psychological Seque-

lae. *Oncology*, **21**, 34-36.

[19] Haley, A.C., Calahan, C., Gandhi, M., West, D.P., Rademaker, A. and Lacouture, M.E. (2011) Skin Care Management in Cancer Patients: An Evaluation of Quality of Life and Tolerability. *Supportive Care in Cancer*, **19**, 545-554. https://doi.org/10.1007/s00520-010-0851-8

[20] Ra, H.S., Shin, S.J., Kim, J.H., Lim, H., Cho, B.C. and Roh, M.R. (2013) The Impact of Dermatological Toxicities of Anti-Cancer Therapy on the Dermatological Quality of Life of Cancer Patients. *The Journal of the European Academy of Dermatology and Venereology*, **27**, e53-e59. https://doi.org/10.1111/j.1468-3083.2012.04466.x

[21] National Cancer Institute (2010) Common Terminology Criteria for Adverse Events (CTCAE). v4.0. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[22] Novello, S., Capelletto, E., Cortinovis, D., Tiseo, M., Galetta, D., Valmadre, G., Casartelli, C., Rapetti, S.G. and Rossi, A. (2014) Italian Multicenter Survey to Evaluate the Opinion of Patients and Their Reference Clinicians on the "Tolerance" to Targeted Therapies Already Available for Non-Small Cell Lung Cancer Treatment in Daily Clinical Practice. *Translational Lung Cancer Research*, **3**, 173-180.

[23] Rosen, A.C., Case, E.C., Dusza, S.W., Balagula, Y., Gordon, J., West, D.P. and Lacouture, M.E. (2013) Impact of Dermatologic Adverse Events on Quality of Life in 283 Cancer Patients: A Questionnaire Study in a Dermatology Referral Clinic. *American Journal of Clinical Dermatology*, **14**, 327-333. https://doi.org/10.1007/s40257-013-0021-0

[24] Saltz, L.B., Meropol, N.J., Loehrer, P.J., Needle, M.N., Kopit, J. and Mayer, R.J. (2004) Phase II Trial of Cetuximab in Patients with Refractory Colorectal Cancer that Expresses the Epidermal Growth Factor Receptor. *Journal of Clinical Oncology*, **22**, 1201-1208. https://doi.org/10.1200/JCO.2004.10.182

[25] Hirayama, K. and Hamada, T. (2017). Influence on the Daily Life of Non-Small Cell Lung Cancer Patients with Skin Toxicity for EGFR-Tyrosine Kinase Inhibitors. *Journal of Japanese Society of Cancer Nursing*, **31**, 181-190. [In Japanese]

[26] Tischer, B., Bilang, M., Kraemer, M., Ronga, P. and Lacouture, M.E. (2018) A Survey of Patient and Physician Acceptance of Skin Toxicities from Anti-Epidermal Growth Factor Receptor Therapies. *Supportive Care in Cancer*, **26**, 1169-1179. https://doi.org/10.1007/s00520-017-3938-7

[27] Clabbers, J.M.K., Boers-Doets, C.B., Gelderblom, H., Stijnen, T., Lacouture, M.E., van der Hoeven, K.J.M. and Kaptein, A.A. (2016) Xerosis and Pruritus as Major EGFRI-Associated Adverse Events. *Supportive Care in Cancer*, **24**, 513-522. https://doi.org/10.1007/s00520-015-2781-y

[28] Butt, Z., Webster, K., Eisenstein, A.R., Beaumont, J., Eton, D., Masters, G.A. and Cella, D. (2005) Quality of Life in Lung Cancer: The Validity and Cross-Cultural Applicability of the Functional Assessment of Cancer Therapy-Lung Scale. *Hematology/Oncology Clinics of North America*, **19**, 389-420. https://doi.org/10.1016/j.hoc.2005.02.009

[29] Zigmond, A.S. and Snaith, R.P. (1983) The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, **67**, 361-370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

[30] Zigmond, A.S., Snaith, R.P. and Kitamura, T. (1993) The Hospital Anxiety and Depression Scale. *Seisinka-Sindangaku*, **4**, 371-372. [In Japanese]

[31] Juliana, F., Jardim, J.R., Fernandes, A.L., Jamnik, S. and Santoro, I.L. (2010) Reliability of the Brazilian Version of the Functional Assessment of Cancer Thera-

py-Lung (FACT-L) and the FACT-Lung Symptom Index (FLSI). *Clinics* (*Sao Paulo*, *Brazil*), **65**, 1247-1251. https://doi.org/10.1590/S1807-59322010001200005

[32] Yanwei, L., Dongying, L., Zhuchen, Y., Ling, L., Yu, Z. and Zhanyu, P. (2017) A Double-Edged Sword: Should Stage IV Non-Small Cell Lung Cancer Patients Be Informed of Their Cancer Diagnosis? *European Journal of Cancer Care*, **26**, e12665. https://doi.org/10.1111/ecc.12665

[33] Morrison, E.J., Novotny, P.J., Sloan, J.A., Yang, P., Patten, C.A., Ruddy, K.J. and Clark, M.M. (2017) Emotional Problems, Quality of Life, and Symptom Burden in Patients With Lung Cancer. *Clinical Lung Cancer*, **18**, 497-503. https://doi.org/10.1016/j.cllc.2017.02.008

[34] Lee, S.H., Lee, K.H. and Chang, S.J. (2018) Do Health Literacy and Self-Care Behaviours Affect Quality of Life in Older Persons with Lung Cancer Receiving Chemotherapy? *International Journal of Nursing Practice*, **24**, e12691. https://doi.org/10.1111/ijn.12691