Original Article

Targeted Therapy-induced Facial Skin Toxicities: Impact on Quality of Life in Cancer Patients

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Received: October 31, 2017, Accepted: November 22, 2017

ABSTRACT

Objective: Targeted therapy-induced facial skin toxicities may reduce overall quality of life (QoL) in cancer patients. We investigated whether facial skin toxicities affect QoL and attempted to identify factors related to QoL in patients with advanced/recurrent cancer. **Methods:** We performed a cross-sectional study in 34 outpatients with advanced/recurrent cancer showing targeted therapy-induced facial skin toxicities in Japan between November 2016 and February 2017. For measurement, we used the Kessler Psychological Distress Scale (K6), Mental Adjustment to Cancer (MAC) Scale, and Dermatology Life Quality Index (DLQI). Data were analyzed using Spearman's rank correlation coefficient. **Results:** Mean DLQI score in 34 patients was 4.59 (standard deviation ± 4.70), which was interpreted as a small effect on a patient's life. Acneiform rash was the most common skin condition noted, followed by xerosis, pruritus, and erythema. Analysis of DLQI scores revealed that symptoms and feelings was the domain most commonly affected among different domains constituting the DLQI. MAC analysis revealed that the fighting spirit score was the highest among MAC scales. We found that age, K6, and fatalism construct in MAC were significantly correlated with total DLQI scores (age: Spearman's $\rho = -0.48$, $P = 0.004$; K6: $\rho = 0.58$, $P < 0.001$; fatalism; $\rho = -0.39$, $P = 0.025$). **Conclusions:** This is the first study investigating targeted therapy-induced facial skin toxicities in cancer patients. Our results suggest potential negative effects of facial skin toxicities on overall QoL in patients with advanced/recurrent cancer in middle and early old age.

Key words: Advanced/recurrent cancer patient, facial skin toxicities, quality of life, targeted therapy

Access this article online

Quick Response Code:

Website: www.apjon.org

DOI: 10.4103/apjon.apjon_74_17

Cite this article as: Yagasaki K, Komatsu H, Soejima K, Naoki K, Kawada I, Yasuda H, *et al.* Targeted Therapy-induced Facial Skin Toxicities: Impact on Quality of Life in Cancer Patients. Asia Pac J Oncol Nurs 2018;5:172-7.

Introduction

In recent years, targeted therapy is expected to improve survival and quality of life (QoL) of cancer patients, including those with advanced cancers of the colon, lungs, and pancreas.[1] Skin toxicities associated with the use of epidermal growth factor receptor (EGFR) inhibitors are the most common adverse effects, which present as an acneiform rash, erythema, xerosis, pruritus, and paronychia in different parts of the body such as the face, neck, chest, abdomen, and thighs.[2-4]

Dermatological adverse events are often unpredictable. Symptomatic treatments such as use of ointments, emollients, proper hygiene, avoidance of irritant stimuli, and self-care are recommended in clinical practice to prevent deterioration of symptoms.[2,4] Although development of rash can be interpreted as a positive finding indicative of clinical response to and thereby benefit of EGFR inhibitors,[1,5] dermatological adverse events negatively affect functional and emotional domains relating to QoL in cancer patients.[1,6,7] It is important to achieve an effective balance between treatment efficacy and dermatological adverse events to maintain a good QoL in cancer survivors undergoing targeted therapy.

The face is a central part of the body and plays an important role in development of body image and self-esteem.[8] Dermatological disorders associated with visible skin conditions such as eczema and acne vulgaris can lead to social isolation, psychosocial problems, and a lowered sense of QoL.[8,9] People with facial skin conditions are likely to experience lower self-esteem, greater anxiety, and withdrawal from social interaction. Cancer patients with facial skin toxicities experience similar problems; however, because these adverse effects are not associated with fatality, they do not receive much attention in cancer patients receiving treatment. Not many studies have focused on facial skin toxicities and their impact on QoL in cancer patients.

This study focused on targeted therapy-induced facial skin toxicities. Understanding the effects of facial skin toxicities on QoL could facilitate the development of optimal care and support for such patients. In addition to acneiform rash, xerosis and pruritus are also important adverse effects of targeted therapies greatly impacting QoL.[10] We performed a cross-sectional study involving cancer patients presenting with these skin toxicities. We aimed to determine whether facial skin toxicities affect QoL and attempted to identify factors related to QoL in patients with advanced cancer.

Methods

Study design

We performed a cross-sectional study at Keio University Hospital in Tokyo, Japan, between November 2016 and February 2017 investigating cancer outpatients presenting with targeted therapy-induced facial skin toxicities. The study was approved by the institutional review boards of the Faculty of Nursing and Medical Care, Keio University (No. 251) and the Keio University School of Medicine (20160180). Registration number: UMIN000024377.

Participants and data collection

Our inclusion criteria were as follows: (1) patients with advanced cancer including recurrence, regardless of cancer type, duration of morbidity, and presence of metastasis; (2) those with facial skin toxicities (e.g. acneiform rash, xerosis, pruritus, and erythema) Grade 1 or above based on the National Cancer Institute Common Terminology Criteria for Adverse Events; (3) patients aged ≥20 years; and (4) patients who could speak and write Japanese. Exclusion criteria were as follows: (1) patients deemed unsuitable for participation in the study following assessment by an attending physician owing to severe anxiety and/or depression, or cognitive disorder; (2) Eastern Cooperative Oncology Group performance status ≥Grade 3. Participants were recruited using convenience sampling at multiple outpatient clinics for patients with cancer at the Keio University Hospital between November 2016 and February 2017. Objectives and study procedure were explained orally and in writing to the candidate patients at the time of their visit by the investigator, and informed consent was obtained from all participants. All participants completed a questionnaire with a research ID (consecutive de-identification), which was sealed in an envelope and delivered in person.

Measurements

Quality of life

QoL was measured using the Japanese version of Dermatology Life Quality Index (DLQI) for which validity and reliability had been established.[11] DLQI is a 10-question questionnaire designed to measure the impact of skin problem in the week prior to consultation on the QoL.[12] This index consists of six domains (Symptoms and feelings, Daily activities, Leisure, Work or school, Personal relationships, and Treatment), rated on a four-point Likert scale ranging from 3, very much to 0, not at all to yield a total score ranging between 0 and 30.[13,14] DLQI scores are interpreted as follows: 0–1 = no effect at all on patient's life, 2–5 = small effect on patient's life, 6–10 = moderate effect on patient's life, 11–20 = very large effect on patient's life, and 21–30 = extremely large effect on patient's life. "Skin problem" of DLQI can be rephrased according to the disease.[14] In this study, we used DLQI with rephrased "facial skin problem."

K6

We used the validated Japanese version of the Kessler Psychological Distress Scale (K6) to measure psychological distress.[15] K6 contains 6 questions relating to a person's emotional state during the month prior to consultation and responses range from 0 (none of the time) to 4 (all of the time).[16,17] The total score ranges between 0 and 24, with higher scores indicating higher levels of psychological distress. The optimal cutoff point for the K6 scale is ≥13 for serious mental illness.[16]

Mental adjustment to cancer scale

The mental adjustment to cancer scale (MAC) is a self-administered scale to measure a predefined set of psychological responses to cancer comprising 40 items and 5 subscales (fighting spirit, helpless/hopeless, anxious preoccupation, fatalism, and avoidance).[18] Higher mean scores among subscales represent greater use of the respective coping mechanism. In this study, we used a Japanese version of the MAC with established reliability and validity in the Japanese population.[19]

Data analysis

Descriptive statistics were used to describe patient characteristics. QoL was measured using the DLQI, psychological distress was measured using the K6 scale, and mental adjustment was measured using the MAC scale. Spearman's rank correlation coefficient was used to assess the correlation between two variables (age, gender, K6, and MAC with DLQI). All tests were two-tailed with $P < 0.05$ considered statistically significant. All analyses were performed using SPSS version 22.0 for Windows software (IBM Japan, Tokyo, Japan).

Results

This study involved 37 patients, but three patients were excluded because two showed deterioration in their condition and one not showed. Thus, we investigated 34 patients who agreed to participate in the study and collected their data (response rate 100%). Patient characteristics are presented in Table 1. We studied 32 patients with lung cancer (94.12%), 1 patient with colon cancer (2.94%), and 1 patient with pancreatic cancer (2.94%). Of the 32 patients, 13 were men (38.24%). Mean age of patients was 65 years (range 44.0–84.0). In terms of occupation, among studied patients, 8 were full-timers or part-timers (23.52%), 11 homemakers (32.35%), and 15 were unemployed or retired (44.12%). Among all skin toxicities reported, acneiform rash was the most common, present in 25 patients (73.53%). Of note, the sum of percentages exceeds 100% because of the presence of multiple toxicities. Treatment included ointments, creams, and locations for self-management in 32 (94.1%) patients.

Table 1: Patient characteristics (n=34)

Variables	*n* (%)
Age (mean, range)	65.0 (44.0-84.0)
Gender	
Female	21 (61.76)
Male	13 (38.24)
Education (years)	
<13	12 (35.29)
≥13	22 (64.71)
Employment status	
Full-timer/part-timer	8 (23.52)
Housewife	11 (32.35)
Unemployed/retired	15 (44.12)
Marital status	
Married	28 (82.35)
Single (divorced/widowed/single)	6 (17.64)
Diagnosis	
Lung cancer	32 (94.12)
Colon cancer	1 (2.94)
Pancreatic cancer	1 (2.94)
Cancer treatment	
Erlotinib	17 (50.00)
Osimertinib	11 (32.35)
Afatinib maleate	3 (8.82)
Others	3 (8.82)
Facial skin toxicities	
Acneiform rash	25 (73.53)
Xerosis	19 (55.88)
Pruritus	10 (29.41)
Erythema	10 (29.41)
Ecxema	9 (26.47)
Pain	5 (14.71)
Scaling	1 (2.94)

The sum of percentages exceeds 100% because of multiple toxicities. SD: standard deviation

Descriptive statistics of dermatology life quality index, Kessler Psychological Distress scale, and mental adjustment to cancer

Mean DLQI score was 4.59 (standard deviation ± 4.70) indicating a small effect on a patient's life. The symptom and feelings domain (1.71 ± 1.75) showed the highest score among DLQI domain scores, followed by daily activities (1.00 ± 1.21), leisure (0.76 ± 1.21), treatment (0.56 ± 0.79), work or school (0.32 ± 0.53), and personal relationships (0.24 ± 0.61). Mean K6 was 5.32 (±6.20), and four patients (11.8%) demonstrated a cutoff value ≥13. Fighting spirit showed the highest score on the MAC scale, followed by anxious preoccupation, fatalism, helpless/hopeless, and avoidance [Table 2].

Table 2: Descriptive statistics of Dermatology Life Quality Index, K6, and mental adjustment to cancer (n=34)

Variables	Mean±SD
DLQI	
Symptom and feeling	1.71±1.75
Daily activities	1.00±1.21
Leisure	0.76±1.21
Work or school	0.32±0.53
Personal relationship	0.24±0.61
Treatment	0.56±0.79
Total	4.59±4.70
K6	5.32±6.20
MAC	
Fighting spirit	43.88±10.43
Helpless/hopeless	9.62±4.07
Anxious preoccupation	23.32±6.24
Fatalism	19.47±5.80
Avoidance	1.68±1.12

SD: Standard deviation, DLQI: Dermatology Life Quality Index, MAC: Mental adjustment to cancer

Correlation of patient characteristics, psychological status, and mental adjustment to cancer with dermatology life quality index

Table 3 shows the correlation of age, gender, K6, and MAC with DLQI. Age was significantly correlated with a total DLQI score ($\rho = -0.48$, $P = 0.004$), as well as multiple DLQI domain scores such as symptoms and feelings (Spearman's $\rho = -0.42$, $P = 0.013$), daily activities ($\rho = -0.39$, $P = 0.023$), leisure ($\rho = -0.51$, $P = 0.002$), and personal relationships ($\rho = -0.41$, $P = 0.016$). Gender was not significantly correlated with DLQI. K6 was significantly correlated with a total DLQI score ($\rho = 0.58$, $P < 0.001$), as well as multiple DLQI domain scores such as symptoms and feelings ($\rho = 0.44$, $P = 0.009$), daily activities ($\rho = 0.68$, $P < 0.001$), leisure ($\rho = 0.62$, $P < 0.001$), and work or school ($\rho = 0.40$, $P = 0.021$). Fatalism showed a significant correlation with a total DLQI score ($\rho = -0.39$, $P = 0.025$).

Discussion

To the best of our knowledge, ours is the first study investigating the impact of targeted therapy-induced facial skin toxicities on QoL in cancer patients. Facial skin toxicities were demonstrated to negatively affect DLQI scores. Based on interpretation of DLQI scores, the total score was found to produce a "small effect on a patient's life." Because the study included patients with acneiform rash, xerosis, pruritus, and erythema, which are not life-threatening conditions, we found that their daily activities did not seem to be seriously disturbed by these conditions compared to the effect of cancer. Mean DLQI total scores obtained from previous studies including cancer patients with overall dermatological adverse effects induced by chemotherapy or targeted therapy were 2.79[20] and 3.49.[21] Compared to these results describing overall skin toxicities, a mean total score of 4.59 obtained in our study was slightly high despite belonging to the same "small effect" category. Nevertheless, the impact of facial skin toxicities cannot be neglected.

The symptoms and feelings domain score was the highest among all DLQI domains. Symptoms included itchy, and painful or stinging, while feelings included embarrassment or self-consciousness regarding facial skin problems. Because facial skin problems are visible to others, patients may experience high levels of self-consciousness, and are likely to be nervous regarding the reaction of others to their problem, which may affect their self-esteem. Thus, it is important to learn to manage symptoms and also develop/learn coping skills to deal with the psychosocial challenges.

K6 was found to be significantly correlated with total DLQI scores and domains of symptoms and feelings, daily activity, leisure, and work or school. Even among noncancer patients, those with acne vulgaris are likely to experience anxiety,[8] and lowered body image, QoL issues, self-esteem, and psychosocial conditions in adolescents and young adults.[22] Furthermore, a qualitative study performed in patients with rash induced by EGFR inhibitors indicates social isolation experienced by these patients.[23] Multiple negative experiences due to skin toxicities may increase psychological distress and avoidance of personnel relationships, which may eventually lead to social isolation.

Fighting spirit was observed to show the highest score on the MAC scale in this study, followed by fatalism; however, only fatalism was seen to be correlated with QoL. Czerw *et al.* have reportedly not used MAC but a mini-MAC (Mini-Scale) and found that fighting spirit was the highest among mental adjustment styles noted in lung cancer patients[24] and in colon cancer patients.[25] These results suggest adoption of positive coping strategies to reduce anxiety or distress. In our study, however, the small sample size might have affected the results, and fighting spirit was not noted to be correlated with QoL.

Age showed a negative correlation with total DLQI scores and domains of symptoms and feelings, daily activities, leisure, and personal relationships. A previous study investigating overall skin toxicities in a younger population (mean age 59.1 years) found that younger patients reported a lower overall QoL than older patients who presented with the same toxicities.[6] Another study reported that women were more affected than men with respect to QoL, because women consider their skin conditions to be "more serious" than men and tend to be more sensitive about disfigurement and cosmetic problems.[21] In this study, gender was not shown to be

Table 3: Correlation of age, gender, K6, or mental adjustment to cancer with Dermatology Life Quality Index

	DLQI						
Variables	**Symptom and feeling**	**Daily activities**	**Leisure**	**Work or school**	**Personal relationship**	**Treatment**	**Total**
Age	−0.42*	−0.39*	−0.51*	-0.16	−0.41*	−0.24	−0.48*
Gender	−0.11	0.03	−0.06	0.30	0.10	−0.08	0.03
K6	0.44*	0.68*	0.62*	0.40*	0.31	0.29	0.58*
MAC							
Fighting spirit	0.11	−0.06	−0.02	−0.22	0.03	0.04	0.01
Helpless/hopeless	−0.01	0.04	0.02	0.17	−0.14	−0.08	−0.06
Anxious preoccupation	0.12	−0.01	0.01	−0.04	−0.07	−0.06	−0.02
Fatalism	−0.32	−0.22	−0.16	−0.16	−0.31	−0.19	−0.39*
Avoidance	0.01	0.01	0.12	−0.08	0.20	−0.12	−0.05

*$P<0.05$. ρ: Spearman's rank correlation coefficient (nonparametric). DLQI: Dermatology Life Quality Index, MAC: Mental adjustment to cancer

significantly correlated with DLQI scores, and although a few young patients were recruited in the study, decreased QoL was observed even in middle and early old-age patients.

Targeted therapy aims at not only improving survival but also maintaining or improving QoL. Collaboration between oncology and dermatology beyond specialties and disciplines is essential to continuously support patients. Oncology and dermatology nurses should understand psychological distress and potential negative effects (e.g. lowered self-esteem) of facial skin toxicities on QoL in cancer patients, and help them manage their symptoms and mitigate the impact on QoL. A patient's real-life issues should be patiently heard, and their families, friends, and colleagues at the workplace should be educated to create an awareness regarding these issues to avoid misunderstandings regarding their skin conditions (e.g. the fact that these skin lesions are therapy-induced adverse effects and not communicable diseases). Such efforts by nurses and physicians would help patients maintain or improve their QoL.

Limitations

Limitations of our study are as follows: (1) Ours was a cross-sectional study design involving a small number of samples. Participants were recruited only at one facility during the study period. (2) Type of cancer studied was limited because 32 of 34 patients investigated were those who had been diagnosed with lung cancer. (3) Severity and types of symptoms associated with facial skin toxicities might change over time since incidence; however, we could not follow/study these changes owing to the cross-sectional design of our study. We propose a longitudinal study be performed from the time of treatment initiation.

Conclusion

The results of this study show that targeted therapy-induced facial skin toxicities negatively affect QoL in cancer patients. Psychological distress, age, and fatalism on the MAC scale were found to be significantly correlated with QoL. Despite the small sample size, this is the first study to focus on targeted therapy-induced facial skin toxicities in cancer patients. The face symbolizes the identity of an individual and is the point of contact with the world during social interaction. Thus, facial skin toxicities in cancer patients produce a diverse and deep-seated impact in such individuals. This preliminary study highlights the need for further investigation of this topic worth pursuing.

Acknowledgment

The authors are grateful to all of the participants.

Financial support and sponsorship

This work has founded by the research grant from Japan Society for the Promotion of Science KAKENHI Grant Number 15H05081.

Conflicts of interest

There are no conflicts of interest.

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