Original Article

Effects of Epidermal Growth Factor Receptor Inhibitor-Induced Dermatologic Toxicities on Quality of Life

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BACKGROUND: Epidermal growth factor receptor (EGFR) inhibitors frequently result in dermatologic toxicities, including rash, xerosis, pruritus, and paronychia. Although the frequency and severity of these events have been described, their effect on health-related quality of life (QoL) remains poorly understood. By using a dermatology-specific questionnaire, the authors examined the effect of these toxicities on QoL. **METHODS:** Patients completed the Skindex-16, a questionnaire that measures the effects on 3 domains of QoL: symptoms, emotions, and functioning. The severity of dermatologic toxicities was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI-CTCAE). Correlations of dermatology QoL scores with NCI-CTCAE grade, skin phototype (SPT), sex, age, type of EGFR inhibitor, and cancer type were investigated. **RESULTS:** Concordant with greater severity of rash grade, there was an increase in median scores for symptoms ($P = .0006$), emotions ($P < .0001$), function ($P = .001$), and overall score ($P < .0001$). There was an inverse correlation between age and emotions ($r = -0.26$; $P = .03$) and overall score ($r = -0.25$; $P = .04$). There was a significant difference between patients aged $\leq$50 years and patients aged >50 years with regard to symptoms ($P = .02$), emotions ($P = .03$), functioning ($P = .04$), and overall score ($P = .02$). There were no significant differences between QoL and SPT, sex, treatment type, or cancer type ($P > .05$). **CONCLUSIONS:** Toxicities, including rash, xerosis, paronychia, and pruritus, adversely affected QoL, and rash was associated with a QoL greater decrease. Younger patients reported lower overall QoL than older patients who had the same toxicities. The current results support using the NCI-CTCAE as a correlative tool for measuring the effects of rash on dermatology-specific QoL. ***Cancer*** **2010;116:3916–23.** © *2010 American Cancer Society.*

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Epidermal growth factor receptor (EGFR) inhibitors (EGFRIs) have emerged as robust antineoplastic agents for advanced solid tumors. These agents are preferred for what is considered a more favorable systemic side-effect profile compared with cytotoxic chemotherapy. Unlike chemotherapy, which affects most replicating cells, EGFRIs target select pathways that are essential for tumor growth and survival. However, in certain tissues, such as skin, hair, and nails, EGFR signaling is essential for normal functioning. Consequently, it is well known that EGFRIs cause dermatologic toxicities, including a papulopustular rash (PPR) in 45% to 100% of patients, xerosis in 7% to 35% of patients, pruritus in 8% to 35% of patients, and paronychia in 12% to 16% of patients.[1-3] Scalp alopecia, trichomegaly of the eyelashes, and increased hair on the face, nares, and eyebrows also have been reported.[4] It has been demonstrated that, if left untreated, these dermatologic adverse events result in EFGRI dose modification in 72% of episodes or discontinuation in 30% of episodes.[5] Therefore, it is essential that clinicians adequately manage dermatologic toxicities related to EGFRIs to ensure compliance with regimens.[3]

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The physical and psychological effects of dermatologic toxicities secondary to EGFRIs can affect patients' health-related quality of life (QoL). Interviews of patients who received EGFRIs have revealed that the physical discomfort—specifically, pain, burning, and skin sensitivity—caused by EGFRI-induced dermatologic toxicities is burdensome and may progress to significantly impact patients' health-related QoL by restricting daily activities and independence.[6] Patients also may experience worry, frustration, depression, and withdrawal from social activities because of dermatologic toxicities.[6] Whether patients can adequately report this information directly as patient-reported outcomes remains a focused area of investigation. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) is a standard tool used by clinicians to report toxic effects of cancer treatment trials. It has been reported that patients and physicians do not agree on the severity of symptom grades for common CTCAE items.[7] Thus, patient self-reporting of symptoms is a possible approach of symptom monitoring in cancer treatment trials for optimal management.[7] Effective treatment of dermatologic adverse effects of EGFRIs may enhance QoL by limiting toxicities, promoting symptom relief, and/or shortening the duration of disability.

An important gap in the literature on QoL and EGFRIs is that the measurement of dermatology-related QoL generally has not been quantified. Consequently, nearly all of the literature on this topic is from anecdotal reports from patient series or clinician observation. It is possible to measure the impact of EGFRI toxicities with existing QoL instruments, especially those that target dermatologic conditions. One such QoL instrument is the Skindex-16, a self-reported, dermatology-specific QoL questionnaire that has undergone reliability and validity testing in skin disorders, including acne and psoriasis.[8] Although the Skindex-16 has not been used previously in relation to EGFRIs, its advantages include item content focused on multiple dimensions of patient experiences living with acute and chronic skin disorders and its ease of administration. More generally, patients in oncology practices are receptive to completing health-related QoL questionnaires, making administration of the Skindex-16, or similar QoL measures feasible.[9]

The objectives of the current study were to establish the effect of EGFRI-induced dermatologic toxicities on QoL and to determine whether patient characteristics are correlated with dermatology-related QoL. If certain demographic features are associated with decreased QoL, then earlier interventions may be implemented to target vulnerable groups. Because the Skindex-16 is reported in 3 domains—symptoms, emotions, and functioning—we also examined which QoL domain was affected most by dermatologic toxicities resulting from EGFRIs. This information may allow for specialized care, whether it is directed medically, psychologically, or socially. In this study, we also investigated the correspondence of physician-assigned NCI-CTCAE grades for EGFRI-induced cutaneous reactions with patient-reported, dermatology-specific QoL, because correspondence between the 2 may suggest the use of the NCI-CTCAE as a surrogate tool to measure the effects of EGFRIs on dermatology-specific QoL. Our findings are intended to demonstrate the effect of dermatologic toxicities on QoL in EGFRI-treated patients.

MATERIALS AND METHODS

Data Collection

Data were collected through a Northwestern University Institutional Review Board-approved, retrospective medical record review of patients who were seen between July 2007 and April 2008 at Northwestern University's Skin and Eye Reactions to Inhibitors of EGFR and Kinases (SERIES) clinic, a specialty referral clinic for patients who have dermatologic toxicities from cancer therapies.[10] Informed consent was waived for the purposes of this retrospective review. Patient data were included in the research dataset if they presented to the clinic with an EGFRI as part of their therapeutic regimen. Patients who were referred for prophylactic treatment of dermatologic toxicity were coded as grade 0. Patients who completed the Skindex-16 at their initial visit were included in the study. For each patient, the following information was collected from the medical record, as available: sex; age; type of EGFRI (cetuximab, erlotinib, lapatinib, panitumumab, or gefitinib); Fitzpatrick skin phototype (SPT); severity of rash, as measured by NCI-CTCAE; pruritus grade; xerosis grade; paronychia grade; alopecia grade; telangiectasia grade; and mucositis grade.

Grading of Dermatologic Adverse Events

Clinical severity grading of dermatologic adverse events was assessed using the version 3.0 of the NCI-CTCAE. Severity of EGFRI-induced PPR was classified according to the NCI-CTCAE acne/acneiform rash grades. Grade 0 refers to no rash. According to the NCI-CTCAE, a grade 1 rash does not require intervention. Intervention is

Table 1. Skindex-16

During the past week, how often have you been bothered by:	↓Never bothered → always bothered↓					
1. Your skin condition itching	☐0	☐1	☐2	☐3	☐4	☐5
2. Your skin condition burning or stinging	☐0	☐1	☐2	☐3	☐4	☐5
3. Your skin condition hurting	☐0	☐1	☐2	☐3	☐4	☐5
4. Your skin condition being irritated	☐0	☐1	☐2	☐3	☐4	☐5
5. The persistence/reoccurrence of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5
6. Worry about your skin condition (*for example*, that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5
7. The appearance of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5
8. Frustration about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5
9. Embarrassment about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5
10. Being annoyed about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5
11. Feeling depressed about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5
12. The effects of your skin condition on your interactions with others (*for example*, interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5
13. The effects of your skin condition on your desire to be with people	☐0	☐1	☐2	☐3	☐4	☐5
14. Your skin condition making it hard to show affection	☐0	☐1	☐2	☐3	☐4	☐5
15. The effects of your skin condition on your daily activities	☐0	☐1	☐2	☐3	☐4	☐5
16. Your skin condition making it hard to work or do what you enjoy	☐0	☐1	☐2	☐3	☐4	☐5

[a]Each item asks the patient the degree to which they have been bothered by a specific aspect of their skin condition in the week before administration of the instrument. The patient answers each question by indicating a number from 0 (never bothered) to 5 (always bothered).

indicated in a grade 2 rash; and grade 3 rash is associated with pain, disfigurement, ulceration, or desquamation.

Both xerosis and cheilitis are categorized as follows: grade 1, asymptomatic; grade 2, symptomatic but does not interfere with activities of daily living; and grade 3, interferes with activities of daily living. Pruritus is classified grade 1 (mild or localized), grade 2 (intense or widespread), and grade 3 (intense or widespread and interferes with activities of daily living). Telangiectasia is categorized using the following scale: grade 1, few; grade 2, moderate number; and grade 3, many and confluent. Alopecia is classified as grade 1 (thinning or patchy) or grade 2 (complete). Both mucositis and paronychia are classified as grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (life-threatening, disabling).

Assessment of QoL Using the Skindex-16

The Skindex-16 is a 16-item, single-spaced, skin-related, QoL instrument that has been validated as an accurate and sensitive measure of how much patients are bothered by their skin conditions.[8] The Skindex-16 instrument is displayed in Table 1. Each item asks patients the degree to which they have been bothered by a specific aspect of their skin condition in the week before administration of the instrument. Patients answer every question with a number ranging from 0 (never bothered) to 6 (always bothered). After the questionnaire is completed, the responses to each item are transformed to a linear scale of 100 that ranges from 0 (never bothered) to 100 (always bothered). Consequently, each item has a minimum score of 0 and a maximum score of 100. In the current study, the Skindex-16 results are reported as an overall score and as 3 domain scores: symptoms, emotions, and functioning. For the overall score, the mean score of all items is calculated. Thus, the overall score has a minimum of 0 and a maximum of 100. Items 1 through 4 on the Skindex-16 pertain to the symptoms domain. The mean of these items is calculated, and a symptoms domain score is determined that also ranges from 0 to 100. Similarly, the emotions domain is based on items 5 through 11, and an emotions domain score is calculated on a scale from 0 to 100. The functioning domain is based on items 12 through 16, and a functioning domain score is calculated in the same manner. Skindex-16 items also are analyzed within each domain to assess the influence of specific items on the overall domain score. The means of the transformed scores for each item are compared statistically within each domain.

Determination of Fitzpatrick SPT

The Fitzpatrick SPT is a classification system for skin phototype that is used widely in dermatology to characterize an individual's susceptibility to sunlight.[11] Sunburn often is observed in patients who have a limited ability to develop inducible melanin pigmentation (tanning) in response to ultraviolet radiation. Darker skinned individuals burn less often and tan with greater ease than lighter skinned individuals. There are 6 phototypes that range from I to VI. Individuals with SPT I have pale, white skin and, in response to sun exposure, burn easily and do not tan; individuals with SPT II have white skin, tan with

difficulty, and burn easily; individuals with SPT III have white skin and tan after an initial sunburn; individuals with SPT IV have light-brown or olive skin and tan easily with sun exposure; individuals with SPT V have brown skin and also tan easily; and individuals with SPT VI have black skin and become darker in the sun.[11]

Statistical Analysis

Skindex-16 scores are reported as medians and semi-interquartile ranges (SIQR) (half the distance between the 25th and 75th percentiles). Repeated-measures analyses of variance were used to compare across the 3 Skindex-16 domain scales (emotions, symptoms, and functioning) and overall scores within the same individuals, and post-hoc *t* tests (Bonferroni adjusted for 3 tests) were used for pairwise comparisons. Repeated-measures analyses of variance also were used to compare across the individual items within each domain scale, and post-hoc *t* tests were used for pairwise comparisons. Spearman correlation coefficients were used to relate the domain and total Skindex-16 scores with age. Wilcoxon rank-sum tests were used to relate the Skindex-16 domain scores and total scores to sex, age (classified as aged $\leq$50 years vs >50), and cancer type. The Kruskal-Wallis test was used to relate the Skindex-16 domain and total scores to NCI-CTCAE toxicity grade (0-3), SPT (I-VI), and type of EGFRI.

RESULTS

Patient Demographics

Sixty-seven patients were included in this study. The mean patient age was 59.1 years (range, 27-86 years), and 79% of patients were aged >50 years. The patients included 61.2% women and 38.8% men. EGFR exposure was as follows: Erlotinib was the most common (received by 49.3% of patients), followed by cetuximab (received by 38.8% of patients), then lapatinib (received by 7.5% of patients), then panitumumab (received by 3% of patients), and then gefitinib (received by 1.5% of patients). The distribution of patients according to Fitzpatrick SPT was as follows: 19.4% of patients had SPT I, 25.4% of patients had SPT II, 13.4% of patients had SPT III, 9% of patients had SPT IV, 7.5% of patients had SPT V, and no patients had SPT VI. SPT was not collected for 25.4% of patients, because it was not documented in the medical record at the time of the patient clinic visit. Patient demographics are summarized in Table 2.

Dermatologic Toxicities

Most patients (82.1%) experienced a PPR; 26.9% of all patients had grade 1 PPR, 47.8% of patients had grade 2 PPR, and 7.5% of patients had grade 3 PPR. A minority of patients (17.9%) did not experience PPR. Of all 67 patients, 26.9% experienced grade 1 pruritus, 13.4% experienced grade 2 pruritus, and the remaining patients (56.7%) did not experience pruritus. Most patients (59.7%) did not sustain xerosis; however, 19.4% of patients had grade 1 xerosis, and 20.9% had grade 2 xerosis. Less than 9% of patients experienced each of the following EGFRI-related reactions: paronychia, alopecia, telangiectasia, mucositis, and cheilitis. Dermatologic toxicities are summarized in Table 2.

Skindex-16 Scores

The study population had a median overall Skindex-16 score of 41.7 (SIQR, 25.0). The highest scores were for the emotions domain (median score, 57.1; SIQR, 32.1), which was significantly higher than the functioning domain (median score, 23.3; SIQR, 26.6; $P < .0001$) but not different from the symptoms domain (median score, 45.8; SIQR, 29.1; $P = .11$).

There were significantly negative Spearman correlations between age and emotions ($r = -0.26$; $P = .03$) and between age and overall score ($r = -0.25$; $P = .04$). There were negative but statistically nonsignificant Spearman correlations between age and symptoms ($P = .10$) and between age and function ($P = .07$). There was a statistically significant difference between patients aged $\leq$50 years and patients aged >50 years with regard to symptoms ($P = .02$), emotions ($P = .03$), function ($P = .04$), and overall score ($P = .02$), and younger patients had higher scores.

There was no statistically significant difference between men and women with regard to symptoms ($P = .75$), emotions ($P = .74$), function ($P = .92$), or overall score ($P = .79$). There was no statistically significant difference between treatment type (erlotinib vs lapatinib vs gefitinib vs cetuximab/panitumumab combined) with regard to symptoms ($P = .44$), emotions ($P = .44$), function ($P = .82$), or overall score ($P = .62$). Cetuximab and panitumumab were analyzed together as monoclonal antibodies with similar toxicity profiles.

There was no statistically significant difference between cancer type (lung vs colorectal vs all other cancer types combined) with regard to symptoms ($P = .82$), emotions ($P = .46$), function ($P = .52$), or overall score ($P = .56$). There was no statistically significant difference

Table 2. Patient Characteristics (N=67)

Characteristic	No. of Patients (%)
Sex	
Men	26 (38.8)
Women	41 (61.1)
Age, y	
Range	27-86 (100)
≤50	14 (20.9)
>50	53 (79.1)
EGFRI	
Cetuximab	26 (38.8)
Erlotinib	33 (49.3)
Gefitinib	1 (1.5)
Lapatinib	5 (7.5)
Panitumumab	2 (3)
Fitzpatrick skin phototype	
I	13 (19.4)
II	17 (25.4)
III	9 (13.4)
IV	6 (9)
V	5 (7.5)
VI	0 (0)
Not recorded	17 (25.4)
EGFRI-related reactions[a]	
PPR	
Grade 0	12 (17.9)
Grade 1	18 (26.9)
Grade 2	32 (47.8)
Grade 3	5 (7.5)
Alopecia	
Grade 0	61 (91)
Grade 1	5 (7.5)
Grade 2	1 (1.5)
Grade 3	0 (0)
Pruritus	
Grade 0	38 (56.7)
Grade 1	18 (26.9)
Grade 2	9 (13.4)
Grade 3	0 (0)
Telangiectasia	
Grade 0	63 (95)
Grade 1	3 (4.5)
Grade 2	1 (1.5)
Grade 3	0 (0)
Xerosis	
Grade 0	40 (59.7)
Grade 1	13 (19.4)
Grade 2	14 (20.9)
Grade 3	0 (0)
Mucositis	
Grade 0	64 (95.5)
Grade 1	1 (1.5)
Grade 2	2 (3)
Grade 3	0 (0)
Paronychia	
Grade 0	64 (95.5)
Grade 1	1 (1.5)
Grade 2	2 (3)
Grade 3	0 (0)
Cheilitis	
Grade 0	66 (98.5)
Grade 1	0 (0)
Grade 2	1 (1.5)
Grade 3	0 (0)

EGFRI indicates epidermal growth factor receptor inhibitor; PPR: papulopustular rash.
[a] There were no grade 4 or grade 5 adverse events.

between SPT (I/II, III/IV, V) with regard to symptoms ($P = .82$), emotions ($P = .99$), function ($P = .90$), or overall score ($P = .95$).

Within the symptoms domain (mean score, 45.3), there was a statistically significant difference between Item 2 (bothered by your condition burning or stinging; mean score, 36.1) and Item 4 (bothered by your condition being irritated; mean score, 51.2; $P = .0017$). Within the emotions domain (mean score, 50.0), there was a statistically significant difference between Item 11 (feeling depressed about your condition; mean score, 35.5) and Item 5 (bothered by the persistence of your condition; mean score, 59.2; $P < .0001$). Finally, within the functioning domain (mean score, 43.0), there was a statistically significant difference between Item 14 (your condition makes it hard to show affection; mean score, 25.4) and Item 15 (bothered by the effects of your condition on your daily activities; mean score, 36.3; $P = .0003$). The full results are displayed in Table 3.

Correlation Between Skindex-16 Scores and NCI-CTCAE Grading of Adverse Events

All Skindex-16 domain scores and overall scores differed significantly among PPR grades 0 through 3 (Table 4), such that median symptoms scores, emotion scores, and functioning scores increased with increasing grade of PPR. These differences were statistically significant for all domains (symptoms domain, $P = .0006$; emotions domain, $P < .0001$; functioning domain, $P = .0001$).

The median Skindex-16 symptoms domain scores for pruritus were as follows: grade 0 pruritus, 25.0; grade 1 pruritus, 41.7; and grade 2 pruritus, 66.7. The latter difference in symptoms domain scores among pruritus grades approached significance ($P = .055$). The median Skindex-16 emotions domain scores for pruritus were as follows: grade 0 pruritus, 31.0; grade 1 pruritus, 57.1; and grade 2 pruritus, 73.8 ($P = .051$). There was no statistically significant difference between pruritus grades for

functioning score ($P = .22$) or for the overall Skindex-16 score ($P = .08$).

The median symptoms domain scores were as follows: grade 0 xerosis, 45.8; grade 1 xerosis, 16.7; and grade 2 xerosis, 58.3. The difference between all xerosis grades with regard to symptoms was significant ($P = .03$). There was no statistically significant difference between xerosis grades for emotions ($P = .16$), functioning ($P = .27$), or overall score ($P = .11$). Because of the small numbers of patients who had paronychia, alopecia, telangiectasia, mucositis, and cheilitis, a statistical analysis of the correlation of each of these adverse effects with the Skindex-16 score could not be performed.

Table 3. Skindex-16 Domain Analysis

Skindex-16 Domain[a]	Mean Score
Symptoms subscale	
1. Itching	49.0
2. Burning or stinging	36.1
3. Hurting	42.0
4. Being irritated	54.2
Subscale mean	45.3
Emotions subscale	
5. Persistence/reoccurrence	59.2
6. Worry	56.2
7. Appearance	58.0
8. Frustration	53.2
9. Embarrassment	39.3
10. Being annoyed	48.8
11. Feeling depressed	36.6
Subscale mean	50.0
Functioning subscale	
12. Affecting interactions with others	30.6
13. Desire to be with people	31.3
14. Show affection	25.4
15. Daily activities	36.3
16. Work or do what you enjoy	33.1
Subscale mean	31.3
Total Skindex-16	43.0

[a] Subscales are domains within the Skindex-16 relating to skin condition; each numbered item queries the effect of skin condition on specified term, and possible mean scores range from 0 to 100.

DISCUSSION

The objective of this research was to determine whether individual patient characteristics are correlated with dermatology-related QoL and the extent to which toxicity grade is associated with worsening QoL when a multidimensional measure is used. The results from this study demonstrate that younger patients have lower overall dermatology-related QoL than older patients who experience similar toxicities. It is noteworthy that emotions domain scores were significantly worse in younger patients despite similar scores for the symptoms and functioning domains. PPR typically is present on areas of the skin that are visible to others, often the face, chest, and back,[12] and it is possible that younger patients experience greater impediment by the highly visible rash during treatment. When age was dichotomized within our data into groups ages <50 years and ≥ 50 years, the younger patients had significantly higher scores in all domains, consistent with published research indicating that QoL is effected more severely among younger cancer patients.[13-16] This underscores the notion that younger patients may be more susceptible

Table 4. Correlation of Skindex-16 Score With National Cancer Institute Common Terminology Criteria for Adverse Events Severity Grade of Papulopustular Rash

	PPR[a]				
Skindex-16 Domain	Grade 0, n=12	Grade 1, n=18	Grade 2, n=32	Grade 3, n=5	*P*
Symptoms					.0006
Median	0	37.5	58.3	58.3	
SIQR (range)	7.3 (0-79)	22.9 (0-100)	25.0 (4-100)	14.6 (46-96)	
Emotions					<.0001
Median	0	59.5	61.9	81.0	
SIQR (range)	2.3 (0-24)	26.2 (0-100)	25.6 (12-100)	2.4 (57-100)	
Functioning					.001
Median	0	30.0	28.3	50.0	
SIQR (range)	0 (0-27)	41.7 (0-100)	31.7 (0-100)	1.7 (40-90)	
Overall					<.0001
Median	0	41.7	52.6	69.8	
SIQR (range)	3.9 (0-30)	26.6 (0-100)	21.4 (8-100)	4.7 (49-86)	

PPR indicates papulopustular rash; SIQR, semi-interquartile range.
[a] There were no grade 4 or grade 5 adverse events.

than older patients to diminished QoL because of dermatologic toxicities from EGFRIs, which may be compounded by the finding reported by Jatoi et al that younger patients also are more susceptible to severe PPR.[17]

Results from the current study indicate that none of the patient characteristics studied, including SPT, sex, type of EGFRI, and tumor-type, were correlated significantly with dermatology-related QoL in patients with dermatologic toxicities. We also observed that emotions were impacted most detrimentally by EGFRI-induced dermatologic toxicities. It is noteworthy that this finding varies from the results of a previously reported, uncontrolled study suggesting that physical discomfort from EGFRI-induced toxicities had the greatest impact on QoL.[6] It appears that the disease-targeted instrument, the Skindex-16, is more sensitive, because it includes mild levels of psychological stress from EGFR toxicities by including terms like *worry* and *frustration*, compared with generic measures like the 36-item Short-Form Health Survey (SF-36). However, the range of physical limitations in the Skindex-16 is more limited compared with that in generic measures.

Further analysis of Skindex-16 items within each domain indicates that, with regard to symptoms, patients are more concerned about irritation than about burning or stinging. With regard to the emotions domain, patients reported that the persistence or recurrence of the skin condition was significantly more important than feeling depressed about the skin condition. This may result from patients being confused by, or unsure of, the relation between the skin condition and the progress of cancer treatment. Finally, within the functioning domain, QoL is impacted most by the effects of the skin condition on daily activities. This finding may be understood through anecdotal patient frustrations, indicating that the toxicities resulting from EGFRIs are a public reminder of their cancer status. Thus, it is important to not discount the impact of these toxicities on the daily life of such patients and the possible concern that the toxicities are related to the status of their cancer. Data collected herein are consistent with case reports indicating that EGFRI-induced PPR has a significantly negative impact on QoL as measured by the Skindex-16. PPR has significant, deleterious effects on physical skin symptoms, emotional well being, and functioning in activities of daily living.

Although the Skindex-16 score provides a quantitative assessment of QoL, it may be difficult for clinicians to extrapolate the importance of a numerical value without a frame of reference. To elucidate this, Skindex-16 scores from patients who experienced PPR were compared with published Skindex-16 reports of patients with eczematous dermatitis and acne vulgaris.[8] The median Skindex-16 symptoms domain score was 58.3 for both grade 2 and grade 3 PPR. In comparison, the mean symptoms domain scores for eczematous dermatitis and acne vulgaris were 42 and 31, respectively. The median emotions domain scores for grade 2 and 3 PPR were 61.9 and 81.0, respectively; and the mean emotions domain scores for eczematous dermatitis and acne vulgaris were 52 and 75, respectively. The median functioning domain scores for grade 2 and 3 PPR were 28.3 and 50.0, respectively; and the mean functioning domain scores for eczematous dermatitis and acne vulgaris were 24 and 38, respectively. Taken as a whole, EGFRI-induced grade 2 and 3 PPR has marked effects on symptoms, emotions, and functioning that are greater than the effects of acne vulgaris and more prominent than those of eczematous dermatitis.

The limitations of this study include the inability to thoroughly discern the impact of individual toxicities on QoL. It is noteworthy that, as a skin-related questionnaire, the Skindex-16 does not specifically address hair, nails, or mucous membranes, which are additional significant targets for EGFRI-induced toxicity. Thus, the Skindex-16 is not likely to adequately reflect alterations in QoL because of toxicities like alopecia, paronychia, and mucositis. Moreover, in the current dataset, we lack the ability to understand the complexity of patient responses to the questionnaire. In short, patients may be responding to a constellation of toxicities as opposed to a focused skin toxicity like PPR, which is aligned most closely with the aims of the Skindex-16 as a cutaneous assessment tool. The higher median symptoms domain scores for grade 0 xerosis (45.8) compared with grade 1 xerosis (16.7) may be attributable to the coexistence of other toxicities that affect QoL, such as rash and hair and nail abnormalities, which are present in 100% of patients on long-term therapy.[18] In addition, although the Skindex-16 values indicated a trend toward a correlation with pruritus grade, the results did not attain statistical significance. Particularly notable was the lack of a correlation between the functioning domain and the severity of toxicity.

Because of these limitations, it would be valuable to develop a QoL measurement tool that is sensitive to the multilayered toxicity profile experienced by patients who receive EGFRI therapy. The development of a validated QoL measure that analyzes each toxicity as an individual entity likely will lead to a more in-depth understanding of

the impact on QoL for all types of skin appendages and dermatology-related toxicities.

The results from this study underscore the need to develop effective treatments for EGFRI-induced dermatologic toxicities so that we can improve QoL and ensure medication adherence. This study also highlights the need for increased awareness of QoL related to these adverse reactions in the dermatologic-oncologic community. In addition, the findings support using the NCI-CTCAE as a correlative tool to measure the effects of PPR on dermatology-specific QoL.

CONFLICT OF INTEREST DISCLOSURES

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