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Using the Skindex-16 and Common Terminology Criteria for Adverse Events to assess rash symptoms: results of a pooled-analysis (N0993)

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Abstract

Background—Historically, skin toxicity has been assessed in prospective clinical trials using the clinician-reported National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). The patient-reported Skindex-16 measures symptoms and perceptions of toxicity. This study was designed to compare information provided by these two measures.

Methods—Data were compiled from three placebo-controlled North Central Cancer Treatment Group studies (N06C4, N03CB, N05C4) having rash prevention as the primary objective. All used the Skindex-16 and CTCAE at baseline, weekly during treatment and during a minimum 2-week follow-up period. Statistical procedures, including Pearson correlations, were utilized to determine relationships between adverse event (AE) grades and Skindex-16 scores.

Results—Four hundred and twelve individual patients provided data (median age, 61; 134 male). Patients' Skindex-16 score results show a 0.9 overall mean (range 0–6 with 6 being worse symptoms), a 0.4 baseline mean (range, 0–4.3) and a 1.3 end-of-treatment mean (range, 0–5.9). Ninety-three, 142 and 177 patients experienced a grade 0, 1 and 2+ CTCAE skin toxicity, respectively. Baseline Skindex-16 scores had relatively low correlation with CTCAE grades. The

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correlation of rash grade with Skindex-16 scores ranged from r=0.49 with the function subscale to r=0.62 with the symptom subscale. The highest correlations of the maximum grade of any dermatological AE with the Skindex-16 were r=0.48 for the total score and r=0.55 for the symptom subscale.

Conclusions—The data reported support the decision to include both measures in a clinical trial to assess the patient experience, as each measure may specifically target varying symptoms and intensities.

Keywords

Skindex-16; CTCAE; Dermatitis; Patient-reported outcomes; Cytotoxic treatment-induced dermatitis

Background

Dermatological adverse events (AEs) are common in cancer treatment. Modalities associated with these events include radiation therapy in patients receiving therapy to the skin [1, 2]. Radiation dermatitis and pruritus result from an inflammatory cascade in the tissues treated, with a decrease in the proliferation of basal cells, endothelial cell injury, and subsequent vasodilatation [3]. The skin reaction may increase in its severity during the course of therapy, often reaching maximal severity at approximately 5 weeks after therapy initiation. Rash also is a major side effect of Epidermal Growth Factor Receptor (EGFR) inhibitors [4–6], which were used in two of the three trials of this analysis.

Typical skin dermatitis trial outcomes include the measurement of AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [7]. The use of these criteria is well documented, and the CTCAE has been a standard clinician-reported assessment tool. The CTCAE provides a severity rating scale (0–5) described using specific physical symptoms and characteristics for rash and other dermatologic events. While this assessment tool is widely used, it may not be appropriate for specific treatment-induced side effects. Lacouture et al. have reported limitations of the CTCAE for assessing rash induced by EGRF inhibitors, stating the use of the CTCAE alone is not appropriate as the AE categories are not comprehensive [8]. Of note is how a clinician selects events to evaluate. A physician may not ask the patient about a specific adverse event unless it is common to the disease treatment modality or if lab results show an issue exists. If the patient is experiencing events not specifically monitored by the physician, the patient may or may not voice the complaint, resulting in the AE not being assessed or reported.

Literature has supported the use of Patient-Reported Outcomes (PROs) as an alternate means to measure patient side effects [9]. In particular, the Skindex-16 may be used for patients to rate skin conditions that have occurred within the previous week. It is a short 16-item patient-completed assessment using numerical analogue scales (0=never bothered to 6=always bothered). Responses to the Skindex-16 are categorized into three subscales: symptom, emotional and functional (Table 1). The Skindex-16 measure may be appropriate for a study since it has been shown to be reliable and valid for general skin diseases [10].

It has been argued that in some circumstance, the use of both an objective clinician-reported CTCAE and a subjective patient-reported PRO is redundant, while other studies have shown the use of CTCAE alone under-reports toxicity, and therefore, a PRO provides supplemental information [11]. They state that the PRO may better capture the patient perspective of the event including amount of bother and/or distress or levels of pain intensity and fatigue. A PRO may also allow the patient to evaluate symptoms other than those being evaluated by the clinician. Basch also agrees that health professionals under-report the incidence and

severity of symptoms compared with patients' own accounts [12]. These results confirm the findings of Parliament et al., in 1985, who determined patients reported significantly more toxicities than had been recorded by their physician for nausea/vomiting ($p<0.05$), diarrhoea/constipation ($p<0.05$), alopecia ($p<0.02$), mucosal reaction ($p<0.01$) and decreased performance status ($p<0.01$) [13]. Parliament suggests that because of this disparity, a self-administered questionnaire appears to be a better way of accurately identifying and reporting treatment toxicities.

This current project explored the relationship between the CTCAE and PROs using the measurement of dermatologic conditions caused by radiation or the use of EGFR inhibitors for cancer treatment. This pooled study compiled individual patient data from three studies conducted by the Mayo Clinic Cancer Center where patients completed the Skindex-16 to discern the effectiveness of this tool in measuring dermato-logical adverse events as compared to the CTCAE.

Methods

Data were compiled from three studies which administered the Skindex-16 to the patient populations: N06C4: A Phase III Randomized Double-Blind Study of Mometasone Furoate versus Placebo in the Prevention of Radiation Dermatitis in Breast Cancer Patients Receiving Radiation Therapy (N=176) [14], N03CB: An Exploratory, Placebo-Controlled Trial of Prophylactic Tetracycline for Gefitinib- or Cetuximab-Induced Skin Rash (or Other Epidermal Growth Factor Receptor (EGFR) Inhibitor-Induced Skin Rash) (N=130) [15], N05C4: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Prophylactic Topical Sunscreen to Prevent Erlotinib- or Cetuximab-Induced Skin Rash [or Other Epidermal Growth Factor Receptor (EGFR) Inhibitor-Induced Skin Rash] (N=116) [16]. All three trials had inclusion criteria of patients being over 18 years of age, having a cancer diagnosis and having ability to complete questionnaires. No patient could have had a rash at the time of randomization. All trials required adverse event and QOL assessments to be administered in a similar fashion. Patients participating in the three trials above provided informed consent prior to inclusion in the study. This study was approved by the Mayo Clinic Institutional Review Board (#09-003103).

Data included were the Skindex-16 results and patient adverse event summaries as measured by the CTCAE v 3.0. Study design indicated Skindex-16 and CTCAE results were to be recorded at baseline and weekly during each study, for at least 8 weeks. Patient baseline demographic data were also compiled.

The Skindex-16 assessment was scored using the tool's scoring algorithm which averages all responses for the total Skindex-16 score. Subscale scores were calculated as follows: symptom subscale as the mean of questions 1–4, emotional subscale as the mean of questions 5–11 and functional subscale as the mean of questions 12–16. The maximum grade of each measured dermatologic event was calculated per patient during the course of the study, as well as the maximum grade of any dermatologic event.

The primary outcome measure was the overall Skindex-16 total score as compared to the maximum grade of dermato-logic adverse events. The primary analysis consisted of Spearman and Pearson Correlational analyses. Secondary outcome measures and analyses compared the Skindex-16 subscale scores to adverse event grades analogous to the primary analysis, compared the Skindex-16 scores and grades between baseline demographic groups to determine the extent to which the symptoms, emotions and functioning were related the population using Wilcoxon, Kruskal–Wallis, chi-square or Fisher exact methodology as appropriate and compared all collected variables using regression analyses.

The combined data sets comprised individual patient-level information. Simple unweighted analytic procedures were performed in an exploratory fashion. Since this study was exploratory in nature, no formal power statement was provided.

Results

The three studies provided data for 412 individual patients (median age, 61; 134 male) (Table 2). Patients' Skindex-16 total score results show an overall mean of 0.9 (range 0–6 with 6 being worse symptoms), baseline mean of 0.4 (range, 0–4.3) and end-of-treatment mean of 1.3 (range, 0–5.9) (Fig. 1). These scores increased over time indicating a worsening of symptoms. The AE profile is pictured in Fig. 2, and the AEs for each individual study are reported in Table 3. Incidence of grade 1 and grade 2 dermatologic AEs increased through 4 weeks of treatment. Incidence of grade 2 AEs increased through 6 weeks of treatment. The maximum grades of any dermatologic AE were 93 with grade 0, 142 with grade 1 and 177 with grade 2 or higher.

Baseline Skindex-16 scores had a very low Pearson correlation with CTCAE grades (r=0.005); much of this is due to the requirement of having no rash prior to starting a study. Overall, the correlation of rash grade with the Skindex-16 scores ranged from r=0.49 with the function subscale to r=0.62 with the symptom subscale. The highest correlations of the maximum grade of any dermatological AE with the Skindex-16 were r=0.48 for the total Skindex-16 score (Fig. 3) and r=0.55 for the symptom subscale. This is consistent with what was seen within the individual treatment trials. Maximum grade correlated with Skindex-16 scores for the prophylactic tetracycline study ranged from 0.43 with the function subscale to 0.64 with the symptom subscale. The prophylactic topical sunscreen study correlation of maximum grade with scores ranged from 0.54 with the function subscale to 0.62 with both total score and the symptom subscale, which was consistent with the rash grade correlation to Skindex-16 scores. The pruritus grade with Skindex-16 scores was slightly lower with a range from 0.45 to 0.53. The mometasone furoate study correlations were lower than the other two studies. Correlation of maximum grade with Skindex-16 scores ranged from 0.33 with the function subscale to 0.52 with the symptom subscale. Correlation of pruritus with the symptom subscale was 0.54. All other correlations of individual toxicity type grade with scores were below 0.45.

A comparison of Skindex-16 scores with baseline covariates indicates that the total score and subscale scores were statistically significant between gender where males reported more symptoms and attributes (all p<0.001). These results were confirmed via simple linear regression.

A direct comparison of clinician-reported dermatologic incidence to patient-reported incidence indicated discrepancies between the two pieces of information. Clinicians reported 117 instances of an AE during the course of all of the trials in the 259 patients expressing no symptoms on the Skindex-16 (Table 4). The majority of these were grade 1. Further, there were 855 instances of patient-reported symptoms on the Skindex-16 in the 392 patients whose clinician did not grade using the CTCAE (Table 5).

Conclusions

The data reported in this study support the inclusion of both measures in a clinical trial to assess the patient clinical trial experience, as patients may not report physical indications of a rash via the Skindex-16, yet a skin condition may exist, and the appearance meets the criteria for grading via the CTCAE. Alternately, the CTCAE criteria may not be met, yet patients may be burdened with rash symptoms identified in the Skindex-16. Correlations

indicate that emotional and functional subscales are independent of CTCAE grades. This study supports the hypothesis that both patient-reported and clinician-reported data are useful in the clinical trial setting.

Discussion

The results of this study indicate that there is a discrepancy in the reporting of symptoms by clinicians and patients. Basch has suggested that "the underlying causes of these discrepancies may lie in the sequence of data transfer...or more likely in the multifaceted dynamics of patient-physician communication" [12]. Regardless of the causality, the reality, as shown in Tables 3 and 4 of this study, is that the current data do support the supposition that the CTCAE and the PRO, in this case the Skindex-16, are supplementary and that patients do report more symptoms. Further, the Skindex-16 allows patient rating of emotional and functional burdens that the CTCAE does not take into account.

A previous analysis on patients from the radiation study (N06C4) alone found the Skindex symptom subscale score to be correlated with CTCAE itching (r=0.53), and Skindex itching correlated with CTCAE itching (r=0.58), but other correlations were very poor (<0.50) [17]. Analysis of EGFR inhibitor trials individually had similar correlative results for the symptom subscale and CTCAE grades, but had higher correlations for the other Skindex subscales with the CTCAE grades. Thus, treatment modality might be an influential characteristic of the pooled patient population.

In an attempt to make the CTCAE more appropriate for EGFR inhibitor studies, the Multinational Association of Supportive Care in Cancer has developed a more advanced assessment tool, the EGFRI-dermatologic AE grading scale, to better quantify the existence of skin-related side effects [8]. While this scale does provide more specificity in the grading criteria, it does not incorporate the patient-perceived emotional and functional impact of the AE; thus, the Skindex-16 would also appear to be an appropriate accompaniment to a trial using this scale.

Based on multiple studies, the National Cancer Institute reports, "There is growing awareness that collecting symptom data directly from patients using patient-reported outcome (PRO) tools can improve accuracy and efficiency of AE data collection." [18]. The PRO-CTCAE items have been developed under a contract from the National Cancer Institute (NCI) to the investigators with the intention that they be available in future NCI trials to allow patients to self-report their own adverse symptoms (NCI contract N02-PC-85002-29; PI: Basch). The items integrate clinician-reported criteria and patient-reported criteria. The PRO CTCAE consists of four general categories of terms: analytic technology-based measurements such as laboratory test or imaging results, objective items such as physical examination results, subjective items reflecting the patient experience and a mixed subjective/objective category that combines patient reporting and clinician interpretation such as drug reactions [19]. Currently a study is being developed at the Mayo Clinic to provide supportive data as part of an accumulating body of evidence for the psychometric integrity of the PRO-CTCAE items and also to provide insights towards possible modifications of individual items.

The eventual use of such an item may resolve some of the discrepancies in reporting, and bring to the forefront issues which concern the patient. Results may facilitate communication regarding emotional and functional impact of symptoms which by themselves may be debilitating to the patient beyond the physical characteristics of the symptoms.

Acknowledgments

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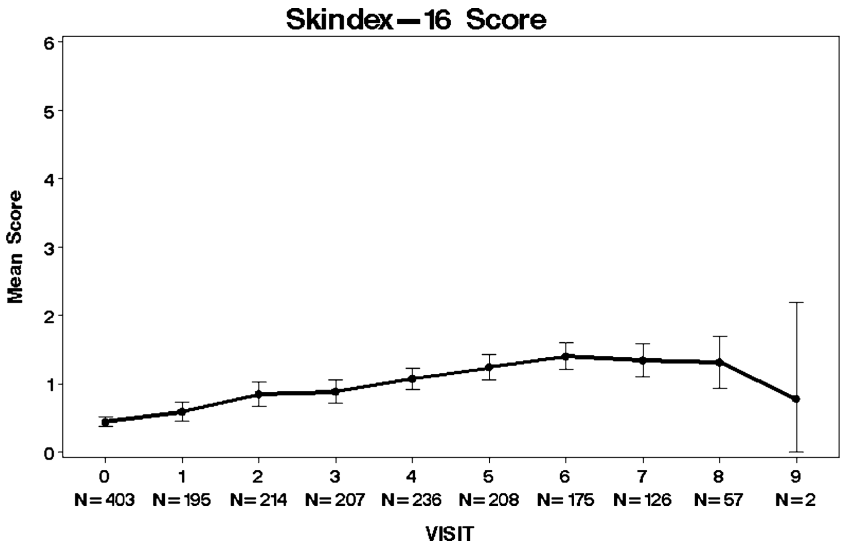

Fig. 1.
Skindex-16 scores

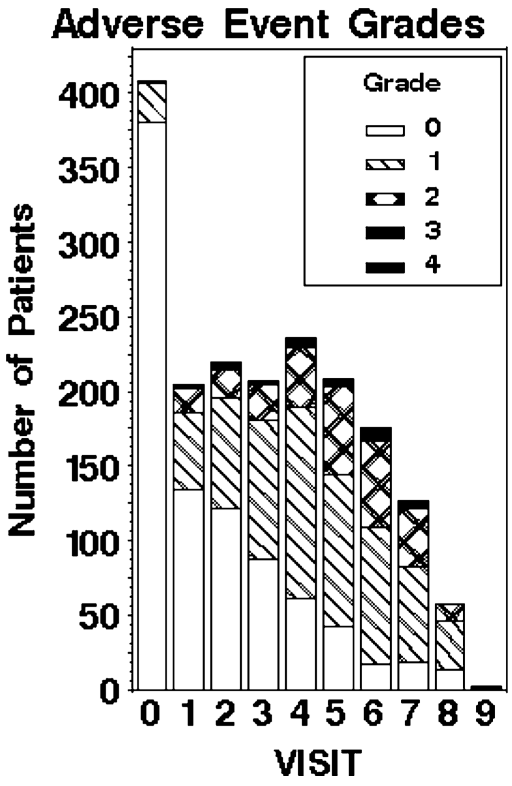

Fig. 2.
Adverse events grades

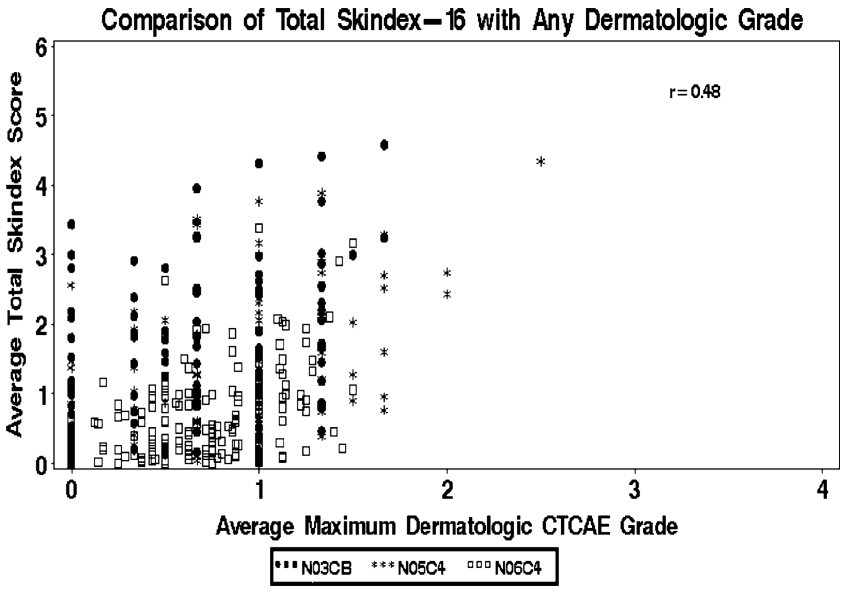

Fig. 3.
Correlation graphic

Table 1

Skindex-16 content

Symptom subscale	Emotional subscale	Functional subscale
1. Skin itching	5. Persistence or recurrence of condition	12. Effect of skin on interaction with others
2. Skin burning or stinging	6. Worry about condition	13. Effect of skin on desire to be with people
3. Skin hurting	7. Appearance of skin	14. Skin making it hard to show affection
4. Skin irritated	8. Frustration about skin	15. Effect of skin on daily activities
	9. Embarrassment about skin	16. Skin making it hard to work/have enjoyment
	10. Annoyed about skin	
	11. Feeling depressed	

Table 2

Baseline characteristics

Age		Race	
Mean (SD)	61.8 (11.5)	White	394 (95.6%)
Median (range)	61 (27–90)	Non-white	18 (4.4%)
Age group		Gender	
≤61	208 (50.5%)	Female	278 (67.5%)
>61	204 (49.5%)	Male	134 (32.5%)
Study			
N03CB: Prophylactic tetracycline			128 (31.1%)
N05C4: Prophylactic topical sunscreen			115 (27.9%)
N06C4: Mometasone furoate			169 (41.0%)

Table 3

Adverse event summary

Prophylactic tetracycline	Grade			
	1	2	3	4
Hand/foot reaction (rxn)			1	
Rash/desquamation	68	58	4	1
Prophylactic topical sunscreen	Grade			
	1	2	3	4
Dry skin		3		
Pruritus	81	17	2	
Rash/desquamation	52	48	9	
Hand/foot rxn		1		
Mometasone furoate	Grade			
	1	2	3	4
RT-induced dermatitis	377	115	11	
Derm skin	69	19	3	
Hypopigmentation	32	4		
Pruritus	322	42	7	
Skin atrophy	8	2		
Skin irritation		4		
Striae	41	1		

Table 4

Discordance between Skindex-16 symptoms and CTCAE grade

Maximum dermatologic CTCAE grade	N03CB (*N*=75 evaluations)	N05C4 (*N*=81 evaluations)	N06C4 (*N*=383 evaluations)	Total (*N*=539 evaluations)
0	70	69	283	422
1	5	10	92	107
2	0	2	7	9
3	0	0	1	1
4	0	0	0	0

Frequency of CTCAE grade for patients with no recorded Skindex-16 symptoms (259 patients, 539 total evaluations)

Table 5

Discordance between CTCAE grade and Skindex-16 measured items

	Individual subscale questions	Number of incidences of event (% of total evaluations)
Symptom subscale questions	Itching	325 (38%)
	Burning/itching	211 (25%)
	Hurting	216 (25%)
	Irritated	261 (31%)
Emotional subscale questions	Persistence/recurrence	246 (29%)
	Worry about skin condition	236 (28%)
	Appearance	280 (33%)
	Frustration	226 (26%)
	Embarrassment	179 (21%)
	Annoyed	207 (24%)
	Depressed	160 (19%)
Functional subscale questions	Interaction with others	153 (18%)
	Desire to be with people	138 (16%)
	Show affection	132 (15%)
	Effect on daily activities	144 (17%)
	Work or do what you enjoy	135 (16%)

Frequency of Skindex-16 measured items for patients with maximum CTCAE AE grade of 0 (392 patients, 876 total evaluations)