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ORIGINAL ARTICLE

A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group

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Abstract
Background Accurate grading of dermatologic adverse events (AE) due to epidermal growth factor receptor (EGFR) inhibitors (EGFRIs) is necessary for drug toxicity determinations, interagent comparisons, and supportive care trials. The most widely used severity grading scale, the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE v4.0), was

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not designed specifically for this class of agents and may result in underreporting and poor grading of distinctive adverse events. We believe a class-specific grading scale is needed to help standardize assessment and improve reporting of EGFRI-associated dermatologic AEs.

Methods The Multinational Association of Supportive Care in Cancer (MASCC) Skin Toxicity Study Group conducted an international multidisciplinary meeting that included 20 clinicians and researchers from academic centers and government agencies. Experts from different disciplines presented current information specific to EGFRI-induced dermatologic toxicities: grading scale development, pharmacovigilance safety reporting, health-related quality of life, patient reporting, and pharmacology. Group discussions, literature reviews, and professional expertise established the theoretical foundation for the proposed grading scale.

Results A new grading system is proposed for the most common events associated with EGFRI-induced dermatologic AEs: papulopustular reaction or acneiform rash, nail changes, erythema, pruritus, xerosis, hair changes, telangiectasias, hyperpigmentation, mucositis, flushing, radiation dermatitis, hyposalivation, and taste changes. The proposed scale maintains consistency with the grading principles and language of the existing CTCAE version 4.0 and MedDRA terminology and includes relevant patient-reported health-related quality of life factors.

Conclusions A grading scale specific to EGFR inhibitor dermatologic AEs is presented for formal integration into future versions of CTCAE and for validation in clinical trial settings. The study group designed this scale to detect and report EGFRI-related toxicities with greater sensitivity, specificity, and range than the scales currently used. This scale should serve as a foundation for efforts to perform objective interdrug comparisons and assessments of supportive care treatment strategies more effectively than with current methods.

Keywords Adverse events · Dermatologic · Skin · Mucosa · Quality of life · EGFR inhibitors · Grading

Background

An adverse event (AE) is any unfavorable and unintended sign (including a laboratory finding), symptom, or disease temporally associated with the use of a medical device, drug, or procedure that may or may not be considered related to such intervention. AE monitoring is a critical component in the assessment of therapies in oncology clinical trials. Anticancer agents are frequently associated with side effects that may impact psychosocial and physical health; these untoward events may further influence clinical outcome and cost of oncology therapy. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 and its preceding versions (CTCAE version 3.0 and Common Toxicity Criteria (CTC) versions 1.0 and 2.0 categorize a broad collection of AEs that are experienced by cancer patients during treatment, and each event has a structured description and rating of severity [1]. Each revision of the CTCAE has sought to include relevant treatment related AEs and to update severity descriptions. However, the evolution of treatments often precede revisions to the CTCAE; this has resulted periodically in delayed recognition and limited capacity to determine precisely the incidence, prevalence, and variability in the presentation of AEs associated with new classes of anticancer agents.

The introduction of novel agents such as epidermal growth factor receptor (EGFR) inhibitors (EGFRIs) that target specific pathways involved in malignant cellular processes generate a constellation of AEs and associated clinicopathologic and scientific questions which are not characterized by the nosology of CTCAE v4.0. As a familiar, available, and well-structured rating system, and in the absence of alternative methods, the CTCAE v4.0 often is the only scale used by cancer investigators to report and study newly recognized AEs of novel classes of anticancer agents. This discordance represents a major obstacle toward the optimal evaluation and utilization of these new therapies [2] as the CTCAE v4.0 AE categories do not reflect all the common AEs associated with the agents. The severity ratings constrain all nonlife-threatening or hospitalization-requiring events into essential dichotomous categories. Though important to the uniform system-wide scaling, these ratings can be ambiguous or fail to capture the resulting degree of physical or psychosocial discomfort [3, 4]. EGFRI dose reductions (60%) or discontinuation (32%) by oncologists have been reported in response to EGFRI-induced dermatologic AEs, which may diminish therapeutic benefits [5].

EGFRIs increasingly have been used in the treatment of a variety of solid tumors [6]. Their effects on tumor control and prolonged survival have led to their approval by the US Food and Drug Administration and the European Medical Evaluation Agency against lung (erlotinib), pancreatic (erlotinib in combination with gemcitabine), colorectal (cetuximab, panitumumab), breast (lapatinib in combination with capecitabine) and head and neck squamous cell cancers (cetuximab in combination with radiotherapy). As EGFR expression has limited tissue distribution, these inhibitors cause fewer systemic and hematopoietic AEs than cytotoxic agents [7]. However, at concentrations necessary for antitumor effects, the coincident inhibition of the EGFR in skin and appendages is believed to result in pathologic alteration of keratinocyte function with consequent inflammation and structural disarray [8]. These mechanism-based effects result in dermatologic AEs: papulopustular eruption (acneiform rash), xerosis, pruritus, hair changes, and nail and periungual

Table 1 Selected dermatologic toxicities to EGFRIs

Drug name	Information source	Dermatologic toxicities								
		Cutaneous and subcutaneous toxicities						Nail changes	Hair modifications	Mucous membrane toxicities	
Cetuximab (Erbitux)	Cunningham et al. [24]	Acne-like rash: all (~80%), grade 3 or 4 (5.2%)			Hypersensitivity reaction: grade 3 or 4 (3.5%)					Stomatitis: grade 3 or 4 (0.9%)	
	Package insert [25]	Acneform rash: all (90%), grade 3 or 4 (8%)		Pruritus: all (11%), grade 3 or 4 (<1%)		Not otherwise specified: all (4%), grade 3 or 4 (0%)		All (16%), grade 3 or 4 (<1%)	Alopecia: all (4%), grade 3 or 4 (0%)	Conjunctivitis: all (7%), grade 3 or 4 (<1%)	
Panitumumab (Vectibix)	Package insert [26]	Erythema: all (65%), grade 3 or 4 (5%)		Pruritus: all (57%), grade 3 or 4 (2%)	Rash: all (22%), grade 3 or 4 (1%)		Dry skin: all (10%), grade 3 or 4 (0%)	Paronychia: all (25%), grade 3 or 4 (2%)	Growth of eyelashes: all (6%), grade 3 or 4 (0%)	Stomatitis: all (7%), grade 3 or 4 (0%)	
	Van Cutsem et al. [31]	Acneform dermatitis: all (57%), grade 3 or 4 (7%)		Skin exfoliation: all (25%), grade 3 or 4 (2%)	Skin fissures: all (20%), grade 3 or 4 (1%)		Acne: all (13%), grade 3 or 4 (1%)	Other: all (9%), grade 3 or 4 (0%)		Mucosal inflammation: all (6%), grade 3 or 4 (<1%)	
Erlotinib (Tarceva)	Shepherd et al. [27]	Rash: all (76%), grade 3–5 (9%)								Stomatitis: all (19%), grade 3–5 (<1%)	Ocular toxic effect: all (28%), grade 3–5 (1%)
	Package insert [28]	Rash: all (75%), grade 3 or 4 (9%)	Pruritus: all (13%), grade 3 or 4 (<1%)	Dry skin: all (12%), grade 3 or 4 (0%)						Conjunctivitis: all (12%), grade 3 or 4: (<1%)	Kerato-conjunctivitis sicca: all (12%), grade 3 or 4: 0%
Lapatinib (Tykerb)	Geyer et al. [29]	Hand-foot syndrome [1]: all (49%), grade 3 or 4 (7%)		Rash [1]: all (27%), grade 3 or 4 (1%)		Dry skin [1]: all (11%), grade 3 or 4 (0%)		Dry skin [1]: all (10%), grade 3 or 4 (0%)	Alopecia: all (23%), grade 3 or 4 (0%)	Mucositis: all (7%), grade 3 or 4 (1%)	
		Package insert [30] Palmar-plantar erythro-dysesthesia [1]: all (53%), grade 3 or 4 (12%)		Rash [1]: all (28%), grade 3 or 4 (2%)							

abnormalities (Table 1) [9, 10]. The incidence and severity of these AEs has been reported to vary by agent (Table 1).

A comprehensive, standardized scale for the reporting of dermatologic AEs in EGFRI-treated patients should enable researchers to conduct more informative controlled studies in this patient population. Studies utilizing a dermatologic AE scale comparing outcomes of specific treatment(s) for dermatologic toxicities, as well as modifications of EGFRI dosages, are expected to standardize findings across clinical trials. To develop a scale better suited for evaluation of antitoxicity interventions and the effects of EGFRI dose modification, the Multinational Association of Supportive Care in Cancer (MASCC) assembled an interdisciplinary panel to devise a scale that adheres to several tenants (Table 2), including (a) use of language consistent with Medical Dictionary for Regulatory Activities (MedDRA) terminology; (b) specific and detailed descriptors of clinical dermatologic events, with grading consistent with CTCAE v4.0 (Fig. 1); (c) inclusion of relevant patient quality-of-life terminology; and (d) the knowledge that the scale would be optimal if subject to validation before widespread implementation. This paper summarizes the efforts of this expert group, with description of EGFRI-induced AEs common with the use of these agents and details the dermatologic scale recommendations developed by the study group.

Methods

Participants

MASCC is an international multidisciplinary organization dedicated to research and education in all measures of supportive care for patients with cancer, regardless of the stage of disease. Supportive care is defined as the prevention and management of physical and psychological symptoms and side effects experienced across the continuum of the cancer experience. The Skin Toxicity Study Group, one of seventeen MASCC study groups, assembled an international, interdisciplinary group of experts in dermatology, medical and supportive oncology, health-related quality-of-life, pharmacovigilance, and clinical scale development. Experts on CTCAE v3.0 and 4.0 grading and EGFRI-induced AEs led presentations and discussions on their respective topics to identify fundamental elements for the development of the new scale. Each work group was assigned to develop the proposed grading system for one particular dermatologic toxicity. Literature searches were performed, and the study group members' prior experience in scale development and dermatologic conditions was utilized. Final revisions are based on consensus review by the entire study group.

Considerations for scale development

The NCI-CTCAE grading scale

The CTCAE v4.0 is a set of descriptive terms for AE reporting in oncology. A grading scale is provided for each AE term. Each CTCAE AE term can and has been mapped to a MedDRA term and code [11]. MedDRA contains clinically validated international medical terminology used by regulatory authorities and the biopharmaceutical industry throughout the entire regulatory process. Currently, it is used in the US, European Union, Canada, and Japan and is mandated for safety reporting in Europe and Japan. MedDRA is managed by the Maintenance and Support Services Organization, an organization that reports to the International Federation of Pharmaceutical Manufacturers and Associations. MedDRA is free for regulators and priced according to company revenue for industry.

In the CTCAE v4.0, grade refers to severity of the AE (Fig. 1). The CTCAE v4.0 displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline, grade 1: mild; grade 2: moderate; grade 3: severe or medically significant but not immediately life threatening; grade 4: life-threatening consequences; grade 5: death. The grading of an event is often used to trigger a supportive care intervention or a dose modification in a particular study, especially grades 3 and 4. The goals of

Table 2 Key factors in the development of the MASCC EGFRI Dermatologic AE scale

Language, terminology, and grading principles to be consistent with NCI-CTCAE v4.0
Language and terminology to be consistent with MedDRA terms and dermatologic nosology
Consideration of subjective measures such as patient HQOL, ADL, and PROs
More specific descriptors of a given dermatologic AE that map to each grade within the NCI-CTCAE
When possible, utilize language or descriptors understandable to patients and providers
Inclusion of time from onset, effect on EGFRI therapy dose
Comply with the FDA mission to describe and track dermatologic toxicities due to EGFRI treatments

HQOL = Health-related quality-of-life, ADL = Activities of daily life, PRO = patient reported outcomes, AE=adverse event. NCI-CTCAE v4.0 Available at https://cabig-kc.nci.nih.gov/Vocab/uploaded_files/4/40/Ctcaev4.pdf

Low grade ← → High grade

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	Moderate	Severe or medically significant but not immediately life-threatening	Life-threatening consequences	Death
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.	Life-threatening consequences; urgent intervention indicated.	Death related to AE.

Fig. 1 NCI-common terminology criteria for adverse events version 4.0, concepts for severity grading (grades 1–5). An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. A *semicolon* indicates "or" within the description of the grade. Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection. *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Available at https://cabig-kc.nci.nih.gov/Vocab/uploaded_files/4/40/Ctcaev4.pdf

the CTCAE v4.0 are to provide a common terminology and classification system for AE reporting, to allow for comparison of AEs across cancer therapeutic clinical trials, and to provide guidance for dose modification on these trials.

Although the present CTCAE v4.0 grading scale can be helpful in categorizing the severity of dermatologic toxicities related to the use of EGFRI therapies, it does not fully characterize the toxicities seen with the EGFRIs, and a better, more specifically defined and validated scale is needed to ensure accurate and meaningful reporting of the dermatologic AEs, especially AEs associated with newer agents. In addition, the CTCAE v4.0 is not validated for skin, nail, and hair toxicities associated with agents such as EGFRIs. A more comprehensive and robust system of grading dermatologic toxicities represents an unmet need to improve clinical research reporting, dosing adjustments during treatment, and management of treatment side effects.

The MASCC EGFRI dermatologic AE scale

Principles followed during the scale development process are listed in Table 2. There were three over-arching considerations in the development of the MASCC EGFRI Dermatologic AE Scale: (1) CTCAE v4.0 items pertinent to EGFRI-induced dermatologic AEs (Table 4) be retained when feasible/desirable, (2) terminology and principles of grading consistent with CTCAE v4.0 be maintained so that events and severity grades can be mapped in order to facilitate reporting by grade for all AEs found in cancer treatment trials, and (3) new AEs proposed to capture EGFRI toxicity use MedDRA terminology. An important additional consideration was that the terminology and means to evaluate each grade be easily available and comprehensible to personnel within an oncology clinic, as these individuals are the most likely users of the new scale.

Consequently, the MASCC EGFRI dermatologic AE scale is consistent with both the CTCAE v4.0 grading scale as well as with MedDRA terminology, and the fundamental severity grading principles and language of the CTCAE are maintained so that translation or mapping may be done grade for grade. For example, a MASCC modification of the standard CTCAE v4.0 scale for "acneiform rash" could be developed for EGFRIs from the existing CTCAE v4.0 drug rash scale. The adapted scale may contain more specific descriptors of the rash, but the grading language for each grade must "line up" or map to each grade in the existing scale. Additionally, some proposed grades are split into multiple levels of severity (e.g., 2A and 2B), but these are collapsible to a single grade (e.g., grade 2) on the existing scale. This consistency between scales allows the proposed scale to be integrated into future revisions of the CTCAE v4.0.

The MASCC Study Group of experts considered multiple objectives for the new EGFRI-specific dermatologic AE scale. Four considerations were apparent: (1) The physician observes only a fraction of the time course of these toxicities relative to the patient's experience; (2) because dermatologic AEs uncommonly reach grade 3 and beyond in severity on the CTCAE v4.0, methods to integrate patient reported outcomes (PRO) are important

[12]. Integrating PROs into the grading system expedites standardization and measure acceptability [13, 14]. To this end, the NCI is developing a patient reported outcome version of CTCAE (called the PRO-CTCAE) which will include PRO versions of multiple CTCAE skin toxicity items. Integrating health-related quality-of-life (HQOL) measures by level of interference in the patients' activities of daily living (ADLs) is one important means by which to stratify relative severity of these AEs. (3) The new scale will be used primarily by oncologists, making the descriptors of AEs separate and specific, with appropriate dermatologic nosology further enhancing joint efforts between oncologists, dermatologists, and others; and (4) as some toxicities such as the papulopustular rash may prove to be pharmacodynamic markers of drug effect, jointly stratifying the lower rash grades by an objective measure would be as important as well as the use of subjective, patient-reported factors. A combination of both subjective and objective measures is thought to be optimal for the MASCC scale, as this would more accurately reflect the impact of dermatologic toxicities on patients.

Results and discussion

Proposed grading scale by type of toxicity

Seventeen dermatologic AEs are included in the proposed scale (Fig. 2), and their grading is based on CTCAE v4.0 and existing dermatology-based grading scales. In addition, members of the panel suggested related items to be included: the specific time to onset of AEs from initiation of EGFRI or combined therapy total dose, and effect on dosing (Table 3).

Papulopustular eruption (acneiform rash)

Approximately 85% of patients treated with EGFRIs develop an eruption consisting of papules and pustules which affect the face and upper body [10]. Skin rash often is associated with symptoms such as pain and itching, which may interfere with ADL. Several limitations of the CTCAE v4.0 rash grading were noted by the MASCC group. Whereas most drug rashes result in a maculopapular eruption affecting the upper body first and progressing to the trunk and extremities, an EGFRI eruption is consistently papulopustular and located in seborrheic areas (i.e., face, upper back, and chest) [15]. Moreover, this rash frequently has been termed acneiform or acne-like even though it has clinical and histological characteristics distinctly different from acne. Therefore, the term papulopustular eruption is recommended by the study group. Further, the criteria currently used by CTCAE v2.0 and v3.0 to determine a grade-3 rash contains items that may not be representative are not characteristic of the EGFRI eruption and/or are imprecise such as desquamation affecting >50% of body surface area (BSA), vesicular eruption and erythroderma; version 3.0 states that rash is associated with pain, disfigurement, ulceration, or desquamation, all of which can be subjective. Grade 4 criteria from rash/desquamation (version 2.0) are also imprecise, as bullous dermatitis may be localized and result from superinfection (i.e., bullous impetigo) and may not convey the intent of this grading severity (consequences, urgent intervention indicated). The study group concludes that, by necessity, the scale should reflect more objective measures (i.e., number of papulopustules, although the count at this time was determined arbitrarily) as well as associated symptoms and the effect on health-related quality of life, including emotions and functioning. Grading also should be amenable to standardized photographic assessment for quantification and reproducibility.

Nail changes

Unlike the papulopustular reaction that occurs within the first 4–8 weeks of drug initiation, nail abnormalities occur after weeks 6–8. Periungual and ungual AEs including paronychia and xerosis with desquamation of the digit tips are reported to occur in up to 58% of patients treated with EGFRIs [3, 16]. Although EGFRI-induced nail abnormalities are generally mild to moderate in severity, if they are not adequately managed, they can result in significant pain, interfere with ADL, and lead to EGFRI dose modification or interruption. Previously, all graded nail abnormalities were contained within a single category. The new version of CTCAE (version 4.0) has divided these events for greater specificity (Table 4). The proposed MASCC scale is more consistent with dermatologists' terminology as it divides nail abnormalities into those of the nail plate, folds, and digit tips and implements classification similar to an established system for nail psoriasis [17]. The expansion of nail abnormality classification allows for grading of onycholysis, periungual erythema, and fissures according to their distinct anatomical site.

Pruritus, xerosis, flushing, and telangiectasias

Pruritus, xerosis, flushing, and telangiectasias are also frequent cutaneous toxicities seen in EGFRI-treated patients (Table 1). These cutaneous reactions can often be managed during treatment and usually do not require dose modification or discontinuation of drug therapy, but they are debilitating when they significantly decrease HQOL. Underreporting and incomplete reporting of flushing,

Adverse Event	Grade 1		Grade 2		Grade 3		Grade 4
Papulopustular eruption (Grading individually for face, scalp, chest or back)	1A Papules or pustules < 5 OR 1 area of erythema or edema <1 cm in size	1B Papules or pustules < 5; OR 1 area of serythema or edema <1cm in size AND pain or pruritus	2A Papules or pustules 6-20; OR 2-5 areas of erythema or edema <1cm in size	2B Papules or pustules 6-20; OR 2-5 areas of erythema or edema <1cm in size AND pain, pruritus, or effect on emotions or functioning	3A Papules or pustules >20; OR more than 5 areas of erythema or edema <1cm in size	3B Papules or pustules >20; OR more than 5 areas of erythema or edema <1cm in size; AND pain, pruritus, or effect on emotions or functioning	-
Nail changes-Nail Plate	Onycholysis or ridging without pain		Onycholysis with mild/moderate pain; any nail plate lesion interfering with instrumental ADL		Nail plate changes interfering with self-care ADL.		-
Nail changes- Nail fold	Disruption or absence of cuticle; OR erythema		Erythematous/tender/painful; OR pyogenic granuloma; OR crusted lesions OR any fold lesion interfering on instrumental ADL		Periungual abscess: OR fold changes interfering with self-care ADL.		-
Nail changes-Digit tip	Xerosis AND/OR erythema without pain		Xerosis AND/OR erythema with mild/moderate pain or stinging; OR fingertip fissures; OR any digit tip lesion interfering with instrumental ADL		Digit tip lesions interfering with self-care ADL		-
Erythema	Painless erythema, blanching; erythema covering <10% BSA		Painful erythema, blanching; erythema covering 10-30% BSA		Painful erythema, nonblanching; erythema covering >30% BSA		-
Pruritus	Mild OR localized, intermittent, not requiring therapy.		2A Moderate localized OR widespread intermittent AND Requiring intervention	2B Moderate localized OR widespread constant AND Requiring intervention	Severe, widespread constant AND interfering with sleep		-
Xerosis	Scaling/flaking covering <10% BSA NO erythema/pruritus/ effect on emotions or functioning		2A Scaling/flaking covering 10-30% BSA + pruritus OR effect on emotions/ functioning	2B Scaling/flaking + pruritus covering 10-30% BSA AND effect on emotions/ functioning + erythema	3A Scaling/flaking covering > 30% BSA AND pruritus AND erythema AND effect on emotions/ functioning AND fissuring/cracking + fissuring/ cracking	3B Scaling/flaking covering >30% BSA AND pruritus AND erythema AND effect on emotions/ functioning AND fissuring/cracking + signs of super infection	-
Hair changes: Scalp hair loss or alopecia	Terminal hair loss <50% of normal for that individual that may or may not be noticeable to others but is associated with increased shedding and overall feeling of less volume. May require different hair style to cover but does not require hairpiece to camouflage		2A: Hair loss associated with marked increase in shedding and 50%-74% loss compared to normal for that individual. Hair loss is apparent to others, may be difficult to camouflage with change in hair style and may require hairpiece.	2B: Marked loss of at least 75% hair compared to normal for that individual with inability to camouflage except with a full wig OR new cicatricial hair loss documented by biopsy that covers at least 5% scalp surface area. May impact on functioning in social, personal or professional situations.	-		--
Hair Changes: disruption of normal hair growth (specify): -Facial hair (diffuse, not just in male beard/mustache areas) -Eyelashes -Eyebrows -Body Hair -Beard and moustache hair	Some distortion of hair growth but does not cause symptoms or require intervention.		2A: Distortion of hair growth in many hairs in a given area that cause discomfort or symptoms that may require individual hairs to be removed.	2B: Distortion of hair growth of most hairs in a given area with symptoms or resultant problems requiring removal of multiple hairs	-		-

Fig. 2 Proposed MASCC Study Group EGFRI-dermatologic AE grading scale

Hair Changes: increased hair changes (specify): -Facial hair (diffuse, not just in male beard/mustache areas) -Eyelashes -Eyebrows -Body Hair -Beard and moustache hair (hirsutism)	Increase in length, thickness and/or density of hair that the patient is able to camouflage by periodic shaving, bleaching or removal of individual hairs.		2A: Increase in length, thickness and/or density of hairs that is very noticeable and requires regular shaving or removal of hairs in order to camouflage. May cause mild symptoms related to hair overgrowth.	2B: Marked increase in hair density, thickness and/or length of hair that requires either frequent shaving or destruction of the hair to camouflage. May cause symptoms related to hair overgrowth. Without hair removal, inability to function normally in social, personal or professional situations.	-		-	
Flushing	1A. Face OR chest, asymptomatic, transient	1B. Any location, asymptomatic, permanent	2A Symptomatic on face, or chest, transient	2B. Symptomatic on face, or chest, permanent	3A Face and chest, transient, symptomatic	3B. Face and chest, permanent, symptomatic	-	
Telangiectasia	One area (<1cm diameter) NOT affecting emotions or functioning		2A 2-5 (1cm diameter) areas NOT affecting emotions or functioning	2B 2-5 (1cm diameter) areas affecting emotions or functioning	More than 6 (1cm diameter) OR confluent areas affecting emotions or functioning		-	
Hyperpigmentation	One area (<1cm diameter) NOT affecting emotions or functioning		2A 2-5 (1cm diameter) areas NOT affecting emotions or functioning	2B 2-5 (1cm diameter) areas affecting emotions or functioning	More than 6 (1cm diameter) OR confluent areas affecting emotions or functioning		-	
Mucositis -Oral -Anal	Mild erythema or edema, and asymptomatic		Symptomatic (mild pain, opiod not required): erythema or limited ulceration, can eat solid foods and take oral medication (Oral mucositis only)		Pain requiring opiod analgesic; erythema and ulceration, cannot eat solids, can swallow liquids (Oral mucositis only)		erythema and ulceration, cannot tolerate PO intake; require tube feeding or hospitalization(Oral mucositis only)	
Radiation dermatitis	Faint erythema or dry desquamation		Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema		Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion		Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	
Hyposalivation	Can eat but requires liquids, no effect on speech		Moderate/thickened saliva: cannot eat dry foods, mild speech impairment (sticky tongue, lips, affecting speech)		No saliva, unable to speak without water, no oral intake without water		-	
Taste	Altered or reduced taste; no impact on oral intake		Altered or reduced taste affecting interest and ability to eat no intervention required		Taste abnormalities, requires intervention		-	

Fig. 2 (continued)

pruritus, and xerosis are common in EGFRI clinical studies [18].

To better represent AEs associated with these categories, the proposed scale has been redefined to address under- and incomplete reporting common in previous studies. More specifically, grade 2 pruritus and xerosis have been subdivided into A and B categories for further precise reporting. Grade 2 pruritus is distinguished by intermittent or constant outbreaks. Grade 2 xerosis is distinguished by comorbidity with erythema, and grade 3 is determined by the presence or absence of superimposed infection. Previous descriptors of telangiectasias are vague and subject to clinical speculation. In the proposed grading scale, severity of telangiectasia is determined by lesion size.

Hair changes (hair loss, disruption of normal hair growth, and increased hair growth)

Inhibition of the EGFR may generate different alterations in hair-bearing areas of the body, with hair loss at the scalp and dense body hair sites, disruption of normal hair growth, and increased hair growth on the face [10]. There is a variable time to presentation of hair loss which is most likely related to the hair growth cycle at the anatomical site involved, but typically hair loss occurs after 3–6 months of therapy [3]. Because EGFRIs are commonly used in combination with cytotoxic chemotherapy, thus, frequently associated with generalized and diffuse hair loss, it is important that the grading scale more accurately reflect the specific type and severity of hair

Table 3 The MASCC Study Group recommended additional modifiers to enhance dermatologic adverse event reporting

Endpoint due to toxicity (DT)	Investigator-directed	Patient-directed
Agent interruption (AIDT)	iAIDT	pAIDT
Agent dose modification (AMDT)	iAMDT	pAMDT
Agent discontinuation (ADDT)	iADDT	pADDT
Death (DDT)	DDT	DDT
Time from initiation (TFI)	TFI	TFI
Total dose (TD)	TD	TD

alteration. This has also been improved in version 4.0 of CTCAE (Table 4).

The Olsen chemotherapy-induced alopecia scale (personal communication from EA Olsen) and the Severity of Alopecia Tool scale [19] are used as a basis for the new MASCC grading. The MASCC Study Group expanded the hair categories to include distinct items for hair loss and increased or disrupted hair growth. Furthermore, hair increases or disruptions are specified for the following anatomical sites: facial hair (diffuse), beard and mustache hair only (hirsutism), eyelashes, eyebrows, and body hair.

The use of standardized baseline photography to provide photographic guidelines in hair-related AEs is suggested. A grade 3 or 4, indicating the need for medical intervention in cases where the psychological impact on the patient is detrimental, is not recommended at this time; however, the necessity of this category may become evident upon validation of the new MASCC grading.

Mucositis, hyposalivation, and taste changes

Treatment with EGFRIs can result in a range of alterations in visible mucosal tissues, namely oral and perianal mucositis, in up to 36% of patients. Clinical severity varies from erythema to deep ulceration of the mucosa, with symptoms ranging from mild tenderness to pain and discomfort at rest and complete inability to tolerate food or fluids or bowel movements. Lip alterations include erythema or erosions of the outer lip and maceration in the angles. The addition of radiotherapy to EGFRIs leads to a greater incidence of severe oral or perianal mucositis in patients with head and neck or rectal cancers, respectively. Currently, the FDA uses the Oral Mucositis Assessment Scale secondarily in validating treatment benefit. Other scales used for the measurement of oral mucositis include the World Health Organization, NCI, Eastern Cooperative Oncology Group, and the Oral Mucositis Index.

In the previous scale, mucositis is considered in a whole body model (anus, esophagus, oral, rectum, and other). The proposed scale focuses on the oral cavity and the anus specifically. Clinically observed AEs remain similar with notable changes in PROs including the patient's level of pain, ability to eat and drink, and recommendations to physicians for interventions. These changes represent an increased focus on the patient's HQOL.

Current literature has not assessed the presence of taste change/loss or saliva change (quantity and texture), which may be underappreciated and may occur with targeted therapies. Therefore, hyposalivation and taste changes are added to the scale in order to provide clinicians and researchers with a standardized way to measure these AEs.

Radiation dermatitis

The proposed scale maintains the original grading of the CTCAE v4.0, with the exception of the removal of grade 5 ("death"). However, combination regimens, in which EGFRIs are administered with radiation, warrant increased attention to radiation-induced skin toxicity. It is noteworthy that the radiosensitizing effect conveyed by EGFRIs on tumor tissues may also occur in skin and mucosa, leading to increased high grade radiation dermatitis and mucositis [20].

Late dermatologic AEs

Currently, CTCAE v4.0 contains a number of terms that may be used to capture late events including fibrosis, telangiectasia and altered pigmentation. As the number of cancer survivors with a history of EGFRI therapies increases, it becomes important to determine and monitor the presence of late dermatologic events. Because there is a putative correlation between early radiation dermatitis and late skin fibrosis [21], it is important to determine whether early EGFRI-induced dermatologic AEs correlate with late effects. Whereas most dermatologic AEs associated with EGFRIs are reversible upon drug discontinuation, postinflammatory changes are frequently observed. These late effects (e.g., hyperpigmentation or telangiectasias) are not specific for EGFRIs, and they may occur as reparative/protective mechanisms following cutaneous injury of multiple etiologies. Future studies are warranted to determine frequency and severity of these late effects and their specific association with EGFRIs.

Table 4 CTCAE v4.0 terms in the dermatology/skin section relevant to EGFRI Dermatologic Adverse Events (grades 1–5)

Adverse event	Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Description	Mild	Moderate	Severe	Life-threatening or disabling	Death related to AE
Papulopustular rash A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back. Unlike acne, this rash does not present with whiteheads or blackheads and can be symptomatic, with itchy or tender lesions		Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL[a]	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL[b]; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Rash acneiform		Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL[a]	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL[b]; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Paronychia A disorder characterized by an infectious process involving the soft tissues around the nail		Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL[a]	Surgical intervention or IV antibiotics indicated; limiting self care ADL[b]	–	–
Nail loss A disorder characterized by loss of all or a portion of the nail		Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL[a]	–	–	–
Nail ridging A disorder characterized by vertical or horizontal ridges on the nails		Asymptomatic; clinical or diagnostic observations only; intervention not indicated	–	–	–	–
Nail discoloration A disorder characterized by a change in the color of the nail plate		Asymptomatic; clinical or diagnostic observations only; intervention not indicated	–	–	–	–
Pruritus		Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL[a]	Intense or widespread; constant; limiting self care ADL[b] or sleep; oral corticosteroid or immunosuppressive therapy indicated	–	
Dry skin		Covering <10% BSA and no associated erythema or pruritus	Covering 10–30% BSA and associated with erythema or pruritus; limiting instrumental ADL[a]	Covering >30% BSA and associated with erythema or pruritus; limiting self care ADL[b]	–	–

Photosensitivity A disorder characterized by an increase in sensitivity of the skin to light	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10–30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death
Telangiectasia A disorder characterized by local dilatation of small vessels resulting in red discoloration of the skin or mucous membranes	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	–	–	–
Flushing A disorder characterized by episodic reddening of the face	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL[a]	Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL[b]	–	–
Alopecia	Hair loss of up to 50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss, but it does not require a wig or hair piece to camouflage	Hair loss of 50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	–	–	–
Hirsutism A disorder characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, mustache, chest, abdomen)	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	–	–	–
Hypertrichosis A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/mustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	–	–	–
Skin hyperpigmentation A disorder characterized by darkening of the skin due to excessive melanin deposition	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	–	–	–
Mucositis oral A disorder characterized by inflammation of the oral mucosal	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Cheilitis A disorder characterized by inflammation of the lip	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL[a]	Severe symptoms; limiting self care ADL[b]; intervention indicated	–	–
Anal mucositis A disorder characterized by inflammation of the mucous membrane of the anus	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL[a]	Severe symptoms; limiting self care ADL[b]	Life-threatening consequences; urgent intervention indicated	Death

Table 4 (continued)

Adverse event	Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Description	Mild	Moderate	Severe	Life-threatening or disabling	Death related to AE
Dermatitis radiation A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation		Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. A semicolon indicates "or" within the description of the grade. An en dash (–) indicates a grade is not available. Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection. Available at https://cabig-kc.nci.nih.gov/Vocab/uploaded_files/4/40/Ctcaev4.pdf

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Additional modifiers during toxicity reporting

In addition to clinical presentation and impact on HQOL/ADL, other factors of importance to toxicity reporting directed by either the physician/investigator or the patient will generate meaningful data relative to the use of EGFRIs. Among these factors is the need for dose modification (reduction, interruption, or discontinuation), death, timing of dermatologic AE from initiation of EGFRI treatment, and relation to total cumulative dose prior to development of the AE. All of these factors using specific nomenclature (Table 3) are to be added when more refined reporting is critical, such as in postmarketing surveillance studies, interagent comparison trials, and antitoxicity interventions.

While the appropriateness of the proposed scale in translating research trial results to clinical practice would be maximized through validity and reliability testing, other considerations are important to take into account during dermatologic AE reporting. Primarily, users of this scale should be aware that different classes of EGFRIs will be associated with different AEs, and updating may be necessary with the introduction of novel agents with different pathway inhibition or toxicity profiles. It is likely that forthcoming EGFRIs are associated with both different AEs than those associated with approved agents and/or with toxicities previously unidentified. Ongoing modifications to reporting and research, therefore, are essential to the proper classification and grading of EGFRI-related AEs.

Summary

EGFR-inhibiting therapeutics trigger new and unusual pathologies that warrant more intensive study, as they can serve as pharmacodynamic markers and are frequently obstacles to consistent EGFRI dosing. For the development of optimal interventions to allow patients to maintain full dose treatment, more detailed and relevant scales than the CTCAE v4.0 dermatology/skin ratings are needed. To address this unmet need in monitoring and reporting, an international multidisciplinary panel of experts comprised a MASCC Study Group from a wide spectrum of relevant disciplines, to develop a new system of grading that accounts for safety reporting and health-related quality of life assessment for measures relative to EGFRI-induced dermatologic toxicities. Additionally, the MASCC Study Group recommends reporting the time to onset of the AE, closer monitoring of late AEs, and awareness of the potential for increased dermatologic toxicity when EGFRI therapy is combined with radiation or other agents. Finally, the patient's HQOL and/or ADL are considered to be important components in the development of this toxicity scale.

Proposed changes include the inclusion of relevant dermatologic nomenclature, as there are distinct clinical

and histological differences between acneiform rash and a papulopustular eruption. Category expansion allows for more specific location, severity, and type of injury reporting consistent with clinical evaluation by dermatologists and is relevant to toxicities seen with EGFRIs. Finally, some of the pruritus and xerosis grades are subdivided to distinguish between the presence and absence of typical coexisting conditions. Increasing attention to AEs in patients receiving EGFRIs suggests that ocular toxicities are frequent and have significant morbidity. Therefore, it is recommended that if CTCAE v4.0 does not specifically address these AEs, a specific grading scale would be a welcome addition in order to better capture these events [22].

The MASCC Study Group proposed scale represents an important step toward redefining dermatological toxicities associated with EGFRI treatment. It is hoped that the new scale will capture the full spectrum of AEs and the associated comorbidity caused by EGFRIs; however, widespread use of the MASCC EGFRI Dermatologic AE scale would be optimal following its confirmation as a valid and reliable outcome measure, in order to facilitate the interpretation and dissemination of AE data. To this end, future steps to consider are validation of the proposed scale in a toxicity intervention or evaluation trial, follow-up for late treatment-associated AEs, and cumulative effects of EGFRIs in combination with other regimens. All of which would optimize the development of interventions to minimize dermatologic AEs, with a consequent improvement in health-related quality-of-life and clinical outcome.

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