MASCC EGFR Inhibitor Skin Toxicity Tool (MESTT)

Multinational Association of Supportive Care in Cancer ™
Skin Toxicity Scale (last updated July, 2009)

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Scale Consensus

A few comments on this scale -

- The scale in these slides represents the latest edition of the scale development process from the MASCC Skin Toxicity Study Group meeting (see date below).

- This set of panels has been endorsed by the MASCC Skin Toxicity Study Group committee, as of September, 2008, and includes all endorsed updates as of July, 2009.

MASCC Skin Toxicity Participants

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Adverse Events

- 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 frequently are associated with side effects that may impact psychosocial and physical health; these untoward events may further influence clinical outcome and cost of oncology therapy.

AE Reporting

- The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.0 and its preceding versions (Common Toxicity Criteria (CTC) versions 1.0, 2.0 and 3.0) 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.
- Scales such as the CTCAE v4.0 are often used in cancer-related Clinical Trials to report a broad range of AEs that can affect treatment (dosing/ therapy discontinuation), treatment outcome and health-related quality of life outcomes (HQOL).

Need for a Comprehensive AE Scale

- The evolution of treatments often precede revisions to the CTCAE; resulting periodically in delayed recognition and limited information on the presentation of AEs associated with new classes of anticancer agents.
- The introduction of novel agents such as epidermal growth factor receptor inhibitors (EGFRIs) generate a constellation of AEs and associated clinicopathologic and scientific questions which are not characterized by the nosology of CTCAE v4.0.
- A comprehensive, standardized scale for the reporting of dermatologic AEs in EGFRI-treated patients should enable researchers to conduct more informative, controlled studies.

Methods for Scale Development

- The Skin Toxicity Study Group 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 v4.0 grading and EGFRI-induced AEs led presentations and discussions on their respective topics to identify fundamental elements for the development of the new scale.
- Small work groups were assigned to develop the grading system for one particular dermatologic toxicity.
- Final revisions are based on consensus review by the entire Study Group.

Factors for Scale Development (1/3)

"Mapping" to CTCAE v4.0

- CTCAE v4.0* items pertinent to EGFRI-induced dermatologic AEs be retained when feasible/desirable.
- Terminology and principles of grading consistent with CTCAE v4.0 be maintained so that events and severity grades can be mapped to the CTCAE v4.0 in order to facilitate reporting by grade for all AEs found in cancer treatment trials.
- New AEs proposed to capture EGFRI toxicity use MedDRA terminology.

the CTCAE v4.0 is available at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf

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Factors for Scale Development (2/3)

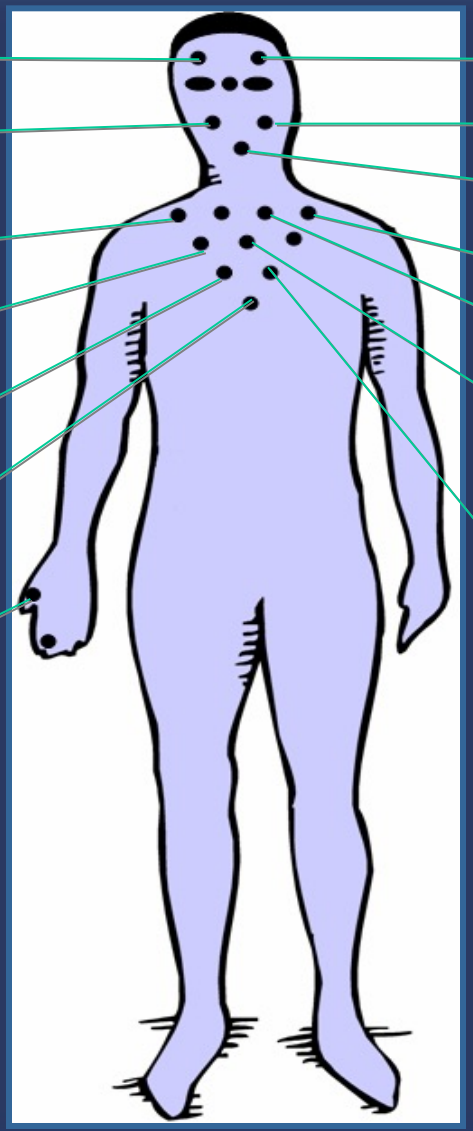
- Health care providers observe only a fraction of the time course of these toxicities relative to the patient's experience.
- Dermatologic AEs uncommonly reach grade 3 and beyond in severity on the CTCAE v4.0.
- Making the descriptors of AEs separate and specific with appropriate dermatologic nosology further enhance joint efforts between oncologists, dermatologists and other health care providers in studying these toxicities.
- Some toxicities (e.g., papulopustular rash) may be pharmacodynamic markers of drug effect, so stratifying the lower grades by objective measures would be as important as the use of subjective, patient-reported factors.

Factors for Scale Development (3/3)

Additional factors in the development of the MASCC Study Group Skin Toxicity scale

- Consideration of subjective measures such as patient HQOL, Activities of Daily Living (ADL) and Patient Reported Outcomes (PROs)
- When possible, utilize language or descriptors understandable to patients and providers
- Inclusion of time, effect on therapy dose of AE
- Comply with the FDA mission to describe and track skin toxicities due to EGFRI treatments

EFGRI Induced Dermatological Toxicities



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MESTT Attributes (1/10)

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 (within the first 4 weeks of drug initiation).

- Symptoms such as pain and itching may interfere with ADL.

MESTT Attributes (2/10)

Improvements for Papulopustular Eruption in the Scale

- Labeling of AE as ‘papulopustular eruption’ instead of ‘acneiform rash’
- More specific nomenclature rash/desquamation for EGFRIs
- Specifying the rash location - EGFRI eruption is consistently papulopustular and located in seborrheic areas (i.e., face, upper back and chest).
- Specific changes to grade 3 to include objective measures (i.e., number of papulopustules) as well as associated symptoms and HQOL.

MESTT Attributes (3/10)

Nail Changes

- 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 (occur 6-8 weeks after drug initiation).
- The scale divides nail abnormalities into those of the nail plate, folds and digit tips and implements classification similar to an established system for nail psoriasis.

MESTT Attributes (4/10)

Pruritus, Xerosis, Flushing and Telangiectasias

- These are frequent cutaneous toxicities seen in EGFRI-treated patients.

- They usually can be managed without drug modification/ discontinuation.

MESTT Attributes (5/10)

Pruritus, Xerosis, Flushing and Telangiectasias

Changes in the scale to correct for under and incomplete reporting include:

- Grade 2 pruritus and xerosis have been subdivided into A and B.
- 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.
- Severity of telangiectasia is determined by lesion size.

MESTT Attributes (6/10)

Hair Changes (hair loss, disruption of normal hair growth, increased hair growth)

- Inhibition of the EGFR will 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 (time to presentation is variable).
- Previous measures used the term ‘alopecia’ to describe all hair loss.

MESTT Attributes (7/10)

Improvements for Hair Changes in the Scale

- The grading scale more accurately reflects the specific type and severity of hair alteration (hair loss, disruption of normal hair growth, increased hair growth).

- Hair increases or disruptions are specified for the following anatomical sites: facial hair (diffuse), eyelashes, eyebrows, body hair and beard or mustache hair (hirsutism).

MESTT Attributes (8/10)

Mucositis, Hyposalivation and Taste Changes

- 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 by mouth or bowel movements.
- Lip alterations include erythema or erosions of the outer lip and maceration in the angles.

MESTT Attributes (9/10)

Improvements for Mucositis, Hyposalivation and Taste Changes in the Scale

- The scale focuses on mucositis of the oral cavity and the anus specifically.
- Notable changes in PROs including the patient's level of pain, ability to eat and drink and recommendations to physicians for interventions to represent an increased focus on the patient's HQOL.
- Hyposalivation and taste changes are added to the scale in order to provide clinicians and researchers with a standardized way to measure these AEs.

MESTT Attributes (10/10)

Improvements for Radiation dermatitis in the Scale

- The scale maintains the original grading of the CTCAE v4.0, with the exception of the removal of grade 5 (‘death’).

- Radiosensitizing effect conveyed by EGFRIs on tumor tissues also may occur in skin and mucosa, leading to increased high grade radiation dermatitis and mucositis.

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Further Considerations for the Scale (1/2)

Late dermatologic AEs

- Currently, CTCAE v4.0 contains a number of terms that may be used to capture late toxicities including fibrosis, telagiectasia 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.
- It is important to determine whether early EGFRI induced dermatologic AEs correlate with late effects.
- Late effects (e.g., hyperpigmentation or telangiectasias) are not specific for EGFRIs and they occur as reparative/ protective mechanisms following cutaneous injury of multiple etiologies.

Further Considerations for the Scale (2/2)

Additional modifiers during toxicity reporting

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 include: 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.

NCI-Common Terminology Criteria for Adverse Events Version 4.0, concepts for severity grading (Grades 1-5)

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.

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Papulopustular Eruption

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	2A Papules or pustules 6-20; OR 2-5 areas of erythema or edema <1cm in size	3A Papules or pustules >20; OR more than 5 areas of erythema or edema <1cm in size	--
	1B Papules or pustules < 5; OR 1 area of erythema or edema <1cm in size AND pain or pruritus	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	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	--

MASCC EGFR Inhibitor Skin Toxicity Tool (2/10)

Nail Changes

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
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 with instrumental AD	Periungual abscess: OR fold changes interfering with self-care ADL	--

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Nail Changes, Erythema, Pruritus

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
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	--

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Xerosis

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
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	3A Scaling/flaking covering > 30% BSA AND pruritus AND erythema AND effect on emotions/ functioning AND + fissuring/ cracking	--
		2B Scaling/flaking + pruritus Covering 10-30% BSA AND effect on emotions/functioning + erythema	3B Scaling/flaking covering >30% BSA AND pruritus AND erythema AND effect on emotions/ functioning AND fissuring/cracking + signs of super infection	

MASCC EGFR Inhibitor Skin Toxicity Tool (5/10)

Hair Changes

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
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.	--	--

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Disruption of normal hair growth

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
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** *(hirsutism)*	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.	--	--

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Increased hair changes, Flushing

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Hair Changes: increased hair growth (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	2A. Symptomatic on face, or chest, transient	3A. Face and chest, transient, symptomatic	--
	1B. Any location, asymptomatic, permanent	2B. Symptomatic on face, or chest permanent	3B. Face and chest, permanent, symptomatic	

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Telangiectasia, Hyperpigmentation

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Telangiectasia	One area (<1cm diameter) NOT affecting emotions or functioning	2A. 2-5 (1cm diameter) areas NOT affecting emotions or functioning	More than 6 (1cm diameter) OR confluent areas affecting emotions or functioning	--
		2B. 2-5 (1cm diameter) 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	More than 6 (1cm diameter) OR confluent areas affecting emotions or functioning	--
		2B. 2-5 (1cm diameter) areas affecting emotions or functioning		

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Mucositis

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
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)

MASCC EGFR Inhibitor Skin Toxicity Tool (10/10)
Radiation dermatitis, Hyposalivation, Taste

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
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	--

Additional Scale Information

- The scale can be accessed at www.mascc.org.
- Please notify MASCC of use of this scale as part of a study or educational program. Permission must be obtained for multiple copy download and a fee might be applied.

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