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Table SI. The comparison of grade criteria between CTCAE grade and grade of dermatological intervention.

	Definition*	CTCAE grade*	Grade of Dermatological Intervention
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.	<p>Grade 1: Papules and/or pustules covering <10% BSA, with or without pruritus or tenderness.</p> <p>Grade 2: Papules and/or pustules covering 10-30% BSA, with or without symptoms of pruritus or tenderness; with psychosocial impact; limiting instrumental activities of daily living; papules and/or pustules covering >30% BSA but mild symptoms.</p> <p>Grade 3: Papules and/or pustules covering >30% BSA, with moderate to severe symptoms; limiting self-care activities of daily living; associated with local superinfection with oral antibiotics indicated.</p> <p>Grade 4: Papules and/or pustules covering any % BSA; with unlimited symptoms; associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences.</p> <p>Grade 5: Death.</p>	<p>Mild: Patients prescribed topical drugs (e.g., topical steroid, topical antibiotics, topical calcineurin inhibitors).</p> <p>Moderate: Patients prescribed one type of oral antibiotics.</p> <p>Severe: Patients who failed prior oral antibiotics therapy and changed the type of oral antibiotics, or those prescribed oral isotretinoin or systemic corticosteroid.</p>
Xerosis	A disorder characterized by flaky and dull skin; the pores are generally fine,	<p>Grade 1: Covering <10% BSA and no associated erythema or pruritus.</p> <p>Grade 2: Covering 10-30% BSA and associated with erythema</p>	<p>Mild: Patients prescribed topical corticosteroid of potency 6 or 7.</p> <p>Moderate: Patients prescribed topical</p>

	the texture is a papery thin texture.	or pruritus; limiting instrumental activities of daily living. Grade 3: Covering >30% BSA and associated with pruritus; limiting self-care activities of daily living.	corticosteroid of potency 4 or 5. Severe: Patients prescribed topical corticosteroid of potency 1, 2, or 3.
Paronychia	A disorder characterized by an infectious process involving the soft tissues around the nail.	Grade 1: Nail fold edema or erythema; disruption of the cuticle. Grade 2: Nail fold edema or erythema with pain; associated with discharge or nail plate separation; limits instrumental activities of daily living; topical or oral anti-infective therapy indicated. Grade 3: Surgical intervention or intravenous antibiotic treatment indicated; limits self-care activities of daily living.	Mild: Patients prescribed topical drugs (e.g., topical corticosteroid, topical antibiotics). Moderate: Patients prescribed oral antibiotics or other non-invasive treatment (e.g., recombinant human EGF ointment, beta-blocker solution, painkillers). Severe: Patients underwent invasive treatments, or patients with “pyogenic granuloma” mentioned in the medical record.
Pruritus	A disorder characterized by an intense itching sensation.	Grade 1: Mild or localized; topical intervention indicated. Grade 2: Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); limiting instrumental activities of daily living. Grade 3: Intense or widespread; constant; limiting self-care activities of daily living or sleep; oral corticosteroid or immunosuppressive therapy indicated.	Mild: Patients prescribed one or two types of antihistamine drugs. Moderate: Patients prescribed three types of antihistamine drugs. Severe: Patients prescribed four types of antihistamine drugs, or patients prescribed oral corticosteroids.

*Adopted from CTCAE version 5.0.

Table SII. Comparison between the recommended management of skin toxicities due to EGFR-TKI in previous studies and the grade of dermatological intervention

	Chu et al., 2017 [†]	Li et al., 2022 [‡]	Grade of Dermatological Intervention
Papulopustular rash	<p>Grade 1</p> <p>(1) Continue EGFR-TKI at current dose</p> <p>(2) Administer topical steroids or topical calcineurin inhibitors (tacrolimus 0.1% ointment or pimecrolimus 1% cream b.i.d.) or alternative topical antibiotics b.i.d. (clindamycin 1–2% or metronidazole 1%, tetracycline 1% or fusidic acid 2%)</p> <p>(3) Try to apply a cream-based ointment or ointment base; avoid alcohol-based ointments</p> <p>Grade 2</p> <p>(1) Continue EGFR-TKI at current dose</p> <p>(2) Administer an oral antibiotic for 4–6 wks (doxycycline 100 mg or minocycline 100 mg q.d. to b.i.d.)</p> <p>(3) Administer topical steroids or topical calcineurin inhibitors (tacrolimus 0.1% ointment or pimecrolimus 1% cream b.i.d.) or alternative topical antibiotics b.i.d. (clindamycin 1–2% or metronidazole 1%, tetracycline 1% or fusidic acid 2%)</p> <p>(4) Administer topical antibiotics if pustules are noted (clindamycin 1–2% or metronidazole 1%, tetracycline 1% or fusidic</p>	<p>Grade 1</p> <p>Continue EGFR inhibitors at the original dose; moisturizing and sunscreen (sun protection factor SPF \geq30); topical antibiotics (clindamycin 1-2% gel, erythromycin 1%, nadifloxacin 1%; fusidic acid 2% or preparations containing metronidazole 0.75%); topical calcineurin inhibitors (tacrolimus 0.1% ointment or pimecrolimus 1% cream bid); reassess after at least 2 weeks or any worsening of symptoms</p> <p>Grade 2</p> <p>Symptom deterioration or patient intolerance (reduction or discontinuation of EGFR inhibitors); moisturizing and sunscreen; topical corticosteroids (hydrocortisone 1-2.5%,</p>	<p>Mild: Patients prescribed topical drugs (e.g., topical steroid, topical antibiotics, topical calcineurin inhibitors).</p> <p>Moderate: Patients prescribed one type of oral antibiotics.</p> <p>Severe: Patients who failed prior oral antibiotics therapy and changed the type of oral antibiotics, or those prescribed oral isotretinoin or systemic corticosteroid.</p>

	<p>acid 2%)</p> <p>(5) Antihistamines can be considered if pruritus is noted</p> <p>Grade 3</p> <p>(1) Interrupt EGFR-TKI and only reinstate (at reduced dose or increasing interval) when skin AE has resolved to Grade 2; oral antibiotics and topical steroids as appropriate; refer patient to dermatologist who specializes in drug-related cutaneous AEs</p> <p>(2) Administer an oral antibiotic for 6 wks (doxycycline 100 mg or minocycline 100 mg q.d. to b.i.d.). If infection is suspected (yellow crusts, purulent discharge, or painful skin/nares):</p> <ul style="list-style-type: none"> • Switch (from oral doxycycline or minocycline) to oral/intravenous broad-spectrum/Gram-negative cover antibiotics • Consider skin swab for bacterial culture <p>(3) May administer short-term oral prednisolone 0.5 mg/kg/d for 1 wk</p> <p>Grade 4</p> <p>(1) Interrupt EGFR-TKI and administer intravenous antibiotics</p>	<p>prednicarbate 0.02% cream, mometasone furoate 0.1%, desoximetasone 0.25%);</p> <p>topical antibiotics (clindamycin 1-2% gel, erythromycin 1%, nadifloxacin 1%; fusidic acid 2% or preparations containing metronidazole 0.75%);</p> <p>topical calcineurin inhibitors (tacrolimus 0.1% ointment or pimecrolimus 1% cream bid.);</p> <p>Oral antibiotics [such as tetracycline (250-500 mg), doxycycline (100-200 mg, bid), oxytetracycline (500 mg, bid) or minocycline (100 mg, bid)]; antihistamines; reassess after at least 2 weeks or any worsening of symptom</p> <p>Grade 3 or 4</p> <p>Temporary discontinuation of EGFR inhibitors; moisturizing and sunscreen; oral antibiotics [such as tetracycline (250-500 mg), doxycycline (100-200 mg, bid), oxytetracycline (500 mg, bid) or minocycline (100 mg, bid)] plus a short course of oral corticosteroid (prednisolone 0.5-1 mg/kg/day for 5-7 days);</p>	
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	<p>(2) Switch from oral antibiotic to broad-spectrum/Gram-negative cover</p> <p>(3) Consider skin swab for bacterial culture</p>	<p>consider oral isotretinoin at low doses (20-30 mg/day); reassess after at least 2 weeks or any worsening of symptoms</p> <p>Grade 5</p> <p>Discontinuation of EGFR inhibitors</p>	
Xerosis	<p>Grade 1</p> <p>(1) Continue EGFR-TKI at current dose</p> <p>(2) Apply moisturizing cream or ointment to face and/or body b.i.d. or more as needed</p> <p>(3) Apply moisturizing cream or Vaseline or urea cream (10%) to the body b.i.d. or more as needed</p> <p>Grade 2</p> <p>(1) Continue EGFR-TKI at current dose</p> <p>(2) Apply moisturizing cream or ointment to face and/or body b.i.d. or more as needed</p> <p>(3) Apply moisturizing cream or Vaseline or urea cream (10%) to the body b.i.d. or more as needed</p> <p>(4) May consider application of topical steroids if eczematous lesions appear</p> <p>Grade 3</p> <p>(1) Interrupt EGFR-TKI treatment. Then resume EGFR-</p>	<p>Use moisturizing emollients several times a day.</p> <p>Avoid bathing with soap and hot water.</p> <p>Use emollients to moisturize the skin after cleansing.</p> <p>Skin dryness with eczematous lesions is treated with topical steroids.</p>	<p>Mild: Patients prescribed topical corticosteroid of potency 6 or 7.</p> <p>Moderate: Patients prescribed topical corticosteroid of potency 4 or 5.</p> <p>Severe: Patients prescribed topical corticosteroid of potency 1, 2, or 3.</p>

	<p>TKI at standard dose or reduced dose or at increased intervals if patient recovers to grade ≤ 2</p> <p>(2) Apply moisturizing cream or ointment to face and/or body b.i.d. or more as needed</p> <p>(3) Apply moisturizing cream or Vaseline or urea cream (10%) to the body b.i.d. or more as needed</p> <p>(4) Start applying topical steroids to eczematous areas b.i.d</p> <p>(5) Antihistamines can be considered if pruritus is noted</p>		
<p>Paronychia</p>	<p>Grade 1</p> <p>(1) Continue EGFR-TKI at current dose; AE can escalate to Grade 2 very quickly</p> <p>(2) Topical ultrapotent steroids or antiseptics or antibiotics (tetracycline 1% ointment) or topical anti-inflammatory agents should be applied as necessary</p> <p>(3) Warm water soaks are beneficial</p> <p>(4) Refer to dermatologist for further assessment and treatment, including potassium permanganate prophylactic soaks</p> <p>Grade 2</p> <p>(1) May continue EGFR-TKI at current dose</p> <p>(2) Start treatment, including oral doxycycline,</p>	<p>Grade 1</p> <p>Continue EGFR inhibitors at original dose; antiseptic hand bath (povidone iodine 1:10, potassium permanganate 1:10000, white vinegar in water 1:1); topical betamethasone valerate (2-3 times, qd); reassess after 2 weeks</p> <p>Grade 2</p> <p>Continue EGFR inhibitors at original dose; silver nitrate solution 20% weekly (administer cryotherapy or other chemical/electric cauterization if granulation); povidone-iodine 2% ointment; topical betamethasone</p>	<p>Mild: Patients prescribed topical drugs (e.g., topical corticosteroid, topical antibiotics).</p> <p>Moderate: Patients prescribed oral antibiotics or other non-invasive treatment (e.g., recombinant human EGF ointment, beta-blocker solution, painkillers).</p> <p>Severe: Patients underwent invasive treatments, or patients with “pyogenic granuloma” mentioned in the medical record.</p>

	<p>minocycline, or cephalexin</p> <p>(3) Topical antibiotics and/or antiseptics should be applied as necessary</p> <p>(4) Apply silver nitrate 20% weekly or administer cryotherapy or other chemical/electric cauterization if granulation has developed</p> <p>Grade 3</p> <p>(1) Interrupt EGFR-TKI treatment. Resume EGFR-TKI at standard dose or reduced dose or at increased intervals if patient recovers to grade ≤ 2. Refer to dermatologist if no improvement. Swab any pus for culture and prescribe oral cephalexin, doxycycline, or minocycline. Administer intravenous antibiotics if cellulitis occurs</p> <p>(2) Continue to apply topical antibiotics and/or antiseptics</p> <p>(3) Apply silver nitrate 20% weekly or administer cryotherapy or other chemical/electric cauterization if granulation has developed.</p> <p>(4) Consider nail avulsion</p>	<p>valerate 0.1% ointment (2-3 times, qd); oral antibiotics are recommended; reassess after 2 weeks</p> <p>Grade 3</p> <p>Temporary discontinuation of EGFR inhibitors; topical clobetasol cream (2-3 times, qd); povidone-iodine 2% ointment; systemic antibiotics oral or intravenously</p> <p>following pathogenic culture; continue to apply topical antibiotics; reassess after 2 weeks</p>	
Pruritus	<p>Grade 1 or 2</p> <p>(1) Continue EGFR-TKI at current dose.</p> <p>(2) Apply topical antipruritics (apply chlorpheniramine strong ointment as needed, or apply pramoxine 1% or doxepin 5% cream</p>	<p>Grade 1 or 2</p> <p>Topical steroids (0.05% clobetasol)</p> <p>Grade 3</p>	<p>Mild: Patients prescribed one or two types of antihistamine drugs.</p> <p>Moderate: Patients prescribed three</p>

	<p>q.i.d.)</p> <p>(3) Apply ice packs or moisturizer</p> <p>(4) Administer oral antihistamines</p> <p>Grade 3</p> <p>(1) Interrupt EGFR-TKI treatment. Then resume EGFR-TKI at standard dose or reduced dose or at increased intervals if patient recovers to grade ≤ 2</p> <p>(2) Apply moisturizing cream or ointment to face and/or body b.i.d. or more as needed</p> <p>(3) Apply moisturizing cream or Vaseline or urea cream (10%) to the body b.i.d. or more as needed</p> <p>(4) Apply topical antipruritics (apply chlorpheniramine strong ointment as needed, or apply pramoxine 1% or doxepin 5% cream q.i.d.)</p> <p>(5) Apply ice packs or moisturizer</p> <p>(6) Administer oral antihistamines, γ-aminobutyric acid agonists (gabapentin or pregabalin), aprepitant or doxepin</p> <p>(7) May consider administering sedative antihistamines if insomnia is occurring</p>	<p>Oral antihistamines (cetirizine, loratadine, etc.) can be used.</p> <p>Additionally, gamma-aminobutyric acid agonists, neurokinin-1 receptor antagonists, antidepressants, corticosteroids, and other drugs can be added for treatment.</p>	<p>types of antihistamine drugs.</p> <p>Severe: Patients prescribed four types of antihistamine drugs, or patients prescribed oral corticosteroids.</p>
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†Adopted from J Formos Med Assoc. 2017 Jun;116(6):413-423.

‡Adopted from Front Oncol. 2022 Feb 10:12:804212.

Table SIII. Comparison between the severity grades based on dermatological intervention and CTCAE grades

	Severity grades based on dermatological intervention				<i>p</i> value
	No	Mild	Moderate	Severe	
CTCAE grades					
Papulopustular rash					<0.001***
G0	33 (89.2)	5 (19.2)	6 (7.1)	2 (7.7)	
G1	3 (8.1)	14 (53.8)	28 (33.3)	7 (26.9)	
G2	1 (2.7)	7 (26.9)	45 (53.6)	13 (50)	
G3	0 (0)	0 (0)	5 (6)	4 (15.4)	
Xerosis					0.008**
G0	75 (100)	22 (78.6)	48 (85.7)	13 (92.9)	
G1	0 (0)	3 (10.7)	1 (1.8)	0 (0)	
G2	0 (0)	3 (10.7)	7 (12.5)	1 (7.1)	
Paronychia					<0.001***
G0	95 (99)	20 (55.6)	12 (35.3)	3 (42.9)	
G1	1 (1)	12 (33.3)	9 (26.5)	2 (28.6)	
G2	0 (0)	4 (11.1)	12 (35.3)	2 (28.6)	
G3	0 (0)	0 (0)	1 (2.9)	0 (0)	
Pruritus					0.124
G0	63 (96.9)	67 (93.1)	8 (80)	24 (92.3)	
G1	2 (3.1)	2 (2.8)	1 (10)	0 (0)	
G2	0 (0)	3 (4.2)	1 (10)	2 (7.7)	

***; $p < 0.001$, **; $p < 0.01$, *; $p < 0.05$

1 st generation	198 (92.5)	50 (67.6)	23.76 (6.73- 83.85)***	134 (88.7)	114 (83.2)	1.57 (0.64- 3.85)	87 (76.3)	161 (92.5)	0.72 (0.29- 1.78)	151 (85.8)	97 (86.6)	0.96 (0.38- 2.40)
2 nd generation	13 (6.1)	6 (31.6)	13.00 (2.74- 61.79)**	8 (5.3)	11 (8.0)	0.97 (0.28- 3.40)	18 (15.8)	1 (0.6)	24.00 (2.68- 214.73)*	12 (6.8)	7 (6.3)	1.06 (0.29- 3.80)
3 rd generation	3 (1.4)	18 (24.3)	Reference	9 (6.0)	12 (8.8)	Reference	9 (7.9)	12 (6.9)	Reference	13 (7.4)	8 (7.1)	Reference

Abbreviation: EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; OR, odds ratio.

Table SV. Association between clinical factors and severity of EGFR-TKI-induced skin toxicities

	Papulopustular rash			OR	Xerosis			OR	Paronychia			OR	Pruritus			OR
	Mild (n=47)	Moderate (n=136)	Severe (n=31)	(95% CI)	Mild (n=41)	Moderate (n=91)	Severe (n=19)	(95% CI)	Mild (n=56)	Moderate (n=45)	Severe (n=13)	(95% CI)	Mild (n=129)	Moderate (n=12)	Severe (n=35)	(95% CI)
Age (years)	66.74 (±10.7)	63.51 (±10.8)	58.48 (±10.6)	0.96 (0.93-0.98)**	62.73 (±11.3)	65.47 (±10.2)	64.89 (±9.9)	1.02 (0.99-1.05)	64.54 (±9.2)	63.88 (±8.3)	64.96 (±9.9)	1.000 (0.96-1.04)	65.22 (±10.6)	65.58 (±9.7)	64.49 (±10.7)	1.00 (0.97-1.03)
Sex																
Male	16 (34)	58 (42.6)	15 (48.4)	1.45 (0.83-2.53)	18 (43.9)	32 (35.2)	6 (31.6)	0.70 (0.36-1.35)	20 (35.7)	17 (37.8)	6 (46.2)	1.40 (0.68-2.87)	49 (38.0)	6 (50.0)	10 (28.6)	0.80 (0.40-1.60)
Female	31 (66)	78 (57.4)	16 (51.6)	Reference	23 (56.1)	59 (64.8)	13 (68.4)	Reference	36 (64.3)	28 (62.2)	7 (53.8)	Reference	80 (62.0)	6 (50.0)	25 (71.4)	Reference
Chronic skin disorder																
Yes	1 (2.1)	3 (2.2)	1 (3.2)	1.30 (0.21-7.89)	0 (0)	4 (4.4)	0 (0)	1.64 (0.22-12.06)	4 (7.1)	0 (0)	1 (7.7)	0.29 (0.04-2.34)	5 (3.9)	0 (0)	1 (2.9)	0.95 (0.07-4.80)
No	46 (97.9)	133 (97.8)	30 (96.8)	Reference	41 (100)	87 (95.6)	19 (100)	Reference	52 (92.9)	45 (100)	12 (92.3)	Reference	124 (96.1)	12 (100)	34 (97.1)	Reference
Prior cytotoxic agent use																
Yes	17 (36.2)	43 (31.6)	12 (38.7)	1.02 (0.57-1.81)	13 (31.7)	26 (28.6)	10 (52.6)	1.46 (0.74-2.90)	17 (30.4)	12 (26.7)	2 (15.4)	0.68 (0.31-1.53)	34 (26.4)	7 (58.3)	12 (34.3)	1.72 (0.86-3.45)
No	30 (63.8)	93 (68.4)	19 (61.3)	Reference	28 (68.3)	65 (71.4)	9 (47.4)	Reference	39 (69.6)	33 (73.3)	11 (84.6)	Reference	95 (73.6)	5 (41.7)	23 (65.7)	Reference
Cancer stage																
II or III	1 (2.2)	5 (3.7)	1 (3.2)	1.28 (0.28-6.00)	1 (2.4)	6 (6.7)	0 (0.0)	1.08 (0.24-4.90)	2 (3.6)	0 (0.0)	0 (0.0)		4 (3.1)	1 (8.3)	1 (2.9)	1.22 (0.21-6.97)
IV	45 (97.8)	131 (96.3)	30 (96.8)	Reference	40 (97.6)	84 (93.3)	19 (100)	Reference	54 (96.4)	45 (100.0)	13 (100.0)		124 (96.9)	11 (91.7)	34 (97.1)	Reference

EGFR-TKI treatment duration (months)	28.6 (±34.5)	26.1 (±28.5)	44.8 (±33.4)	1.01 (1.00-1.02)*	29.1 (±26.1)	30.6 (±33.8)	30.9 (±31.3)	1.00 (0.99-1.01)	23.5 (±19.6)	27.8 (±23.4)	27.5 (±20.5)	1.01 (0.99-1.03)	27.8 (±31.8)	23.5 (±20.4)	32.0 (±30.6)	1.00 (0.99-1.01)
EGFRi generation																
1 st generation	45 (95.7)	125 (91.9)	28 (90.3)	0.75 (0.07-7.62)	38 (92.7)	79 (86.8)	17 (89.5)	0.42 (0.11-1.63)	45 (80.4)	36 (80.0)	6 (46.2)	0.30 (0.08-1.12)	109 (84.5)	12 (100.0)	30 (85.7)	1.99 (0.44-9.05)
2 nd generation	2 (4.3)	8 (5.9)	3 (9.7)	0.77 (0.10-16.8)	2 (4.9)	6 (6.6)	0 (0.0)	0.33 (0.05-2.24)	8 (14.3)	6 (13.3)	4 (30.8)	0.53 (0.12-2.38)	9 (7.0)	0 (0.0)	3 (8.6)	1.90 (0.27-13.30)
3 rd generation	0 (0.0)	3 (2.2)	0 (0.0)	Reference	1 (2.4)	6 (6.6)	2 (10.5)	Reference	3 (5.4)	3 (6.7)	3 (23.1)	Reference	11 (8.5)	0 (0.0)	2 (5.7)	Reference

CI, confidence interval; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitor; OR, odds ratio.

Table SVI. The relationship between the severity of skin toxicities and the response of lung cancer to the first generation EGFR-TKIs

	Response to 1 st generation EGFR-TKI			OR (95% CI)
	Progressive Disease	Stable Disease	Complete Response or Partial Response	
Papulopustular rash				2.29 (1.18-4.45)*
Mild	39 (25.7)	1 (4.5)	1 (11.1)	
Moderate	93 (61.2)	17 (77.3)	5 (55.6)	
Severe	20 (13.1)	4 (18.2)	3 (33.3)	
Xerosis				1.38 (0.65-2.94)
Mild	31 (30.7)	3 (18.7)	2 (28.6)	
Moderate	60 (59.4)	11 (68.8)	4 (57.1)	
Severe	10 (9.9)	2 (12.5)	1 (14.3)	
Paronychia				0.69 (0.23-2.04)
Mild	36 (51.4)	3 (37.5)	3 (100.0)	
Moderate	28 (40.0)	5 (62.5)	0 (0.0)	
Severe	6 (8.6)	0 (0.0)	0 (0.0)	
Pruritus				1.21 (0.73-2.01)
Mild	83 (72.2)	11 (64.7)	6 (75.0)	
Moderate	11 (9.6)	1 (5.9)	0 (0.0)	
Severe	21 (18.2)	5 (29.4)	2 (25.0)	

* $p < 0.05$

Abbreviation: CI, confidence interval; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitor; OR, odds ratio