Management of dermatologic side effects

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Introduction

- Clear evidence that rash presence/severity correlates with response
- May compromise quality of life and require to minimize impact on drug dose and quality of life
- Rash is the most common reported side effect to EGFR Inhibitor treatments

. Rosell R, et al. Ann Oncol. 2008;19:362-369.
. Van Cutsem E, et al. J Clin Oncol. 2007;25:1658-1664.
. Geyer CE, et al. N Engl J Med. 2006;355:2733-2743

Cutaneous complications of targeted drug therapies

Molecular target(s)	Agent	Class	FDA-approved indication	Cutaneous side effects
EGFR	Cetuximab (Erbitux)	mAb	CRC	• Papulopustular rash • Xerosis, fissures and pruritus • Nail and nailfold changes: paronychia/ pariungual granulation tissue • Hair changes: Hair loss on scalp / inflammatory hair loss/ hypertrichosis/ trichomegaly/ trichiasis • In-field radiation toxicity
	Panitumumab (Vectibix)	mAb	CRC	
	Erlotinib (Tarceva)	TKI	NSCLC, pancreatic cancer	
	Gefitinib (Iressa)	TKI	NSCLC	
	Afatinib (Gilotrif)	TKI	NSCLC	

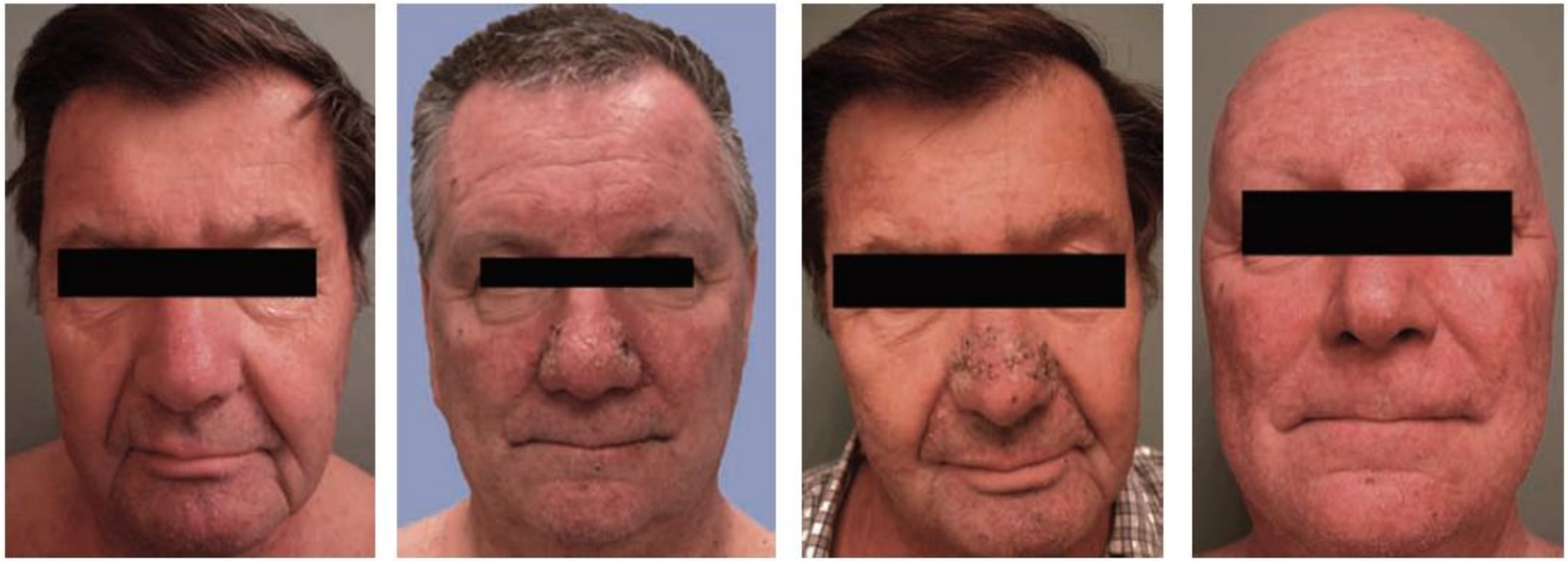
- Adopted from Cancer.net & AJR Am J Roentgenol. 2013 March ; 200(3): 475–483.

Papulopustular rash

- Acneiform erutpion
- Presents within 2 weeks
- Most common skin side effects
  - Gefitinib 44%, erlotinib, 49-75% , cetuximab and panitumumab 90%
- Without comedones, usually itchy
- Response to anti-inflammatory drugs, not to anti-acne agents
- Face, upper trunk, but lower legs and dorsal arms as well

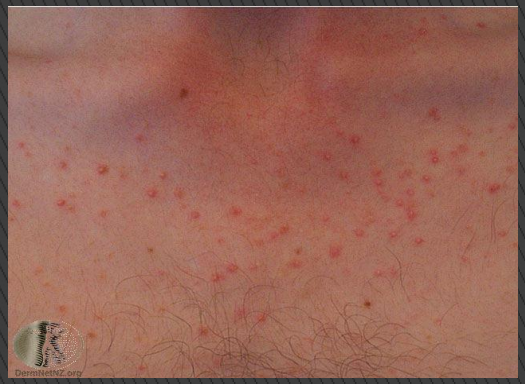
Lacouture Me et al. Curr opin oncol 2011, 23: 343-351

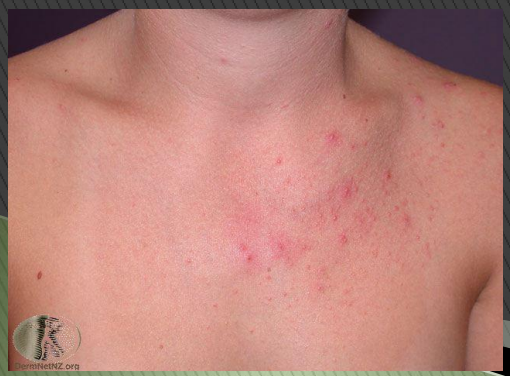
Papulopustular Rash

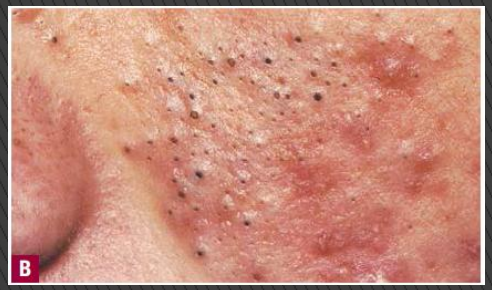


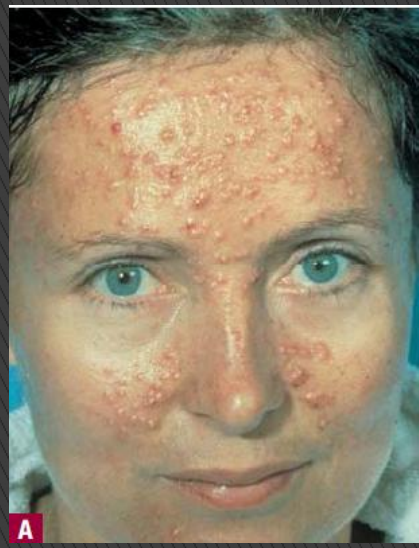
DDx

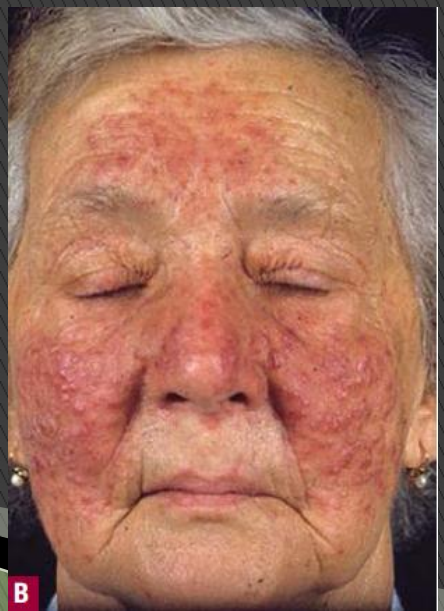
- Seborrhea
- Acne vulgaris
- Rosacea
- Pityrosporum folliculitis



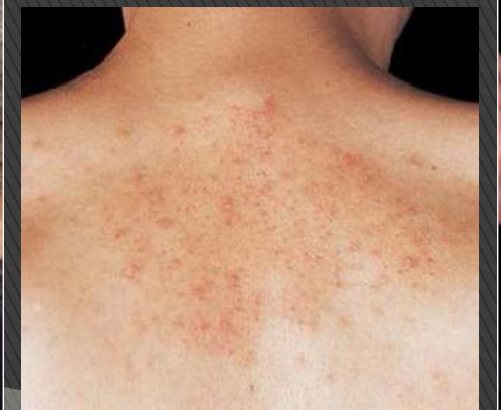


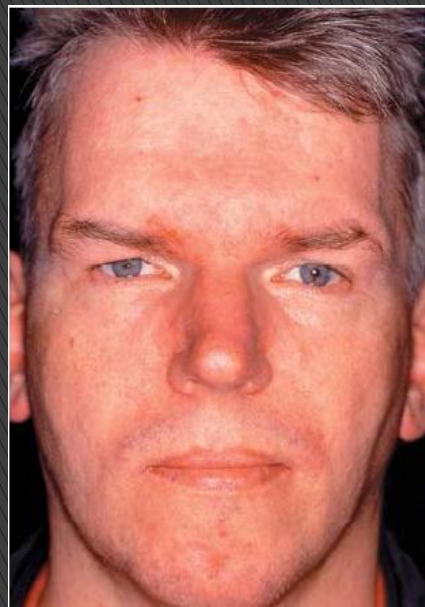






Fitzpatrick's dermatology in general medicine, 7th ed.

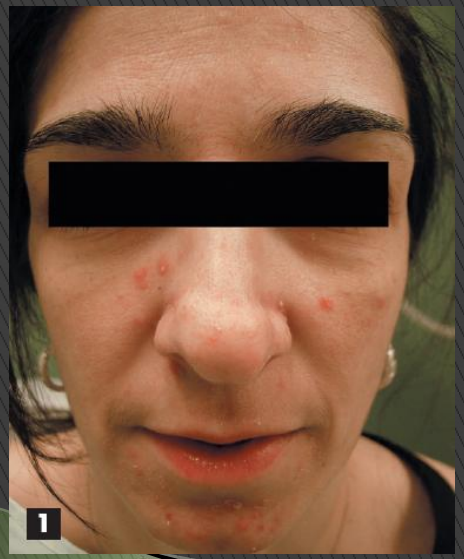


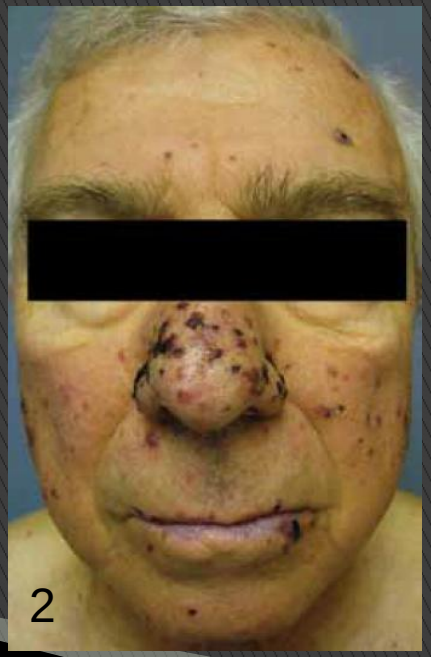


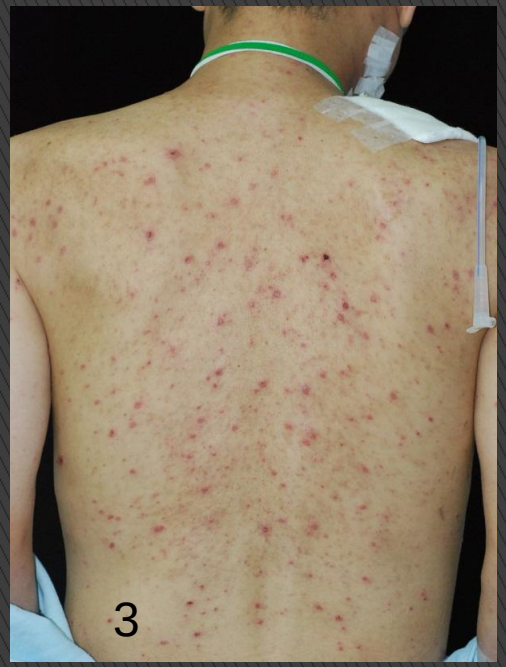
http://www.dermnetnz.org/

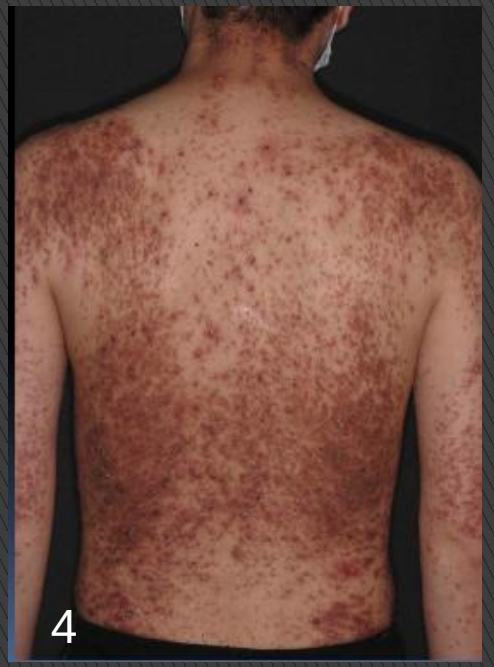
Comment termiology criteria for adverse events (CTCAE) 4.03 Grading

DISORDER	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Rash, acneiform *Definition:* a disorder characterized by an eruption of papules and pustules, typically appearing in the face, scalp, upper chest, and back	Papules and/or pustules covering < 10% of BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10%–30% of BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering > 30% of BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection, with oral antibiotics indicated	Papules and/or pustules covering any % of 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









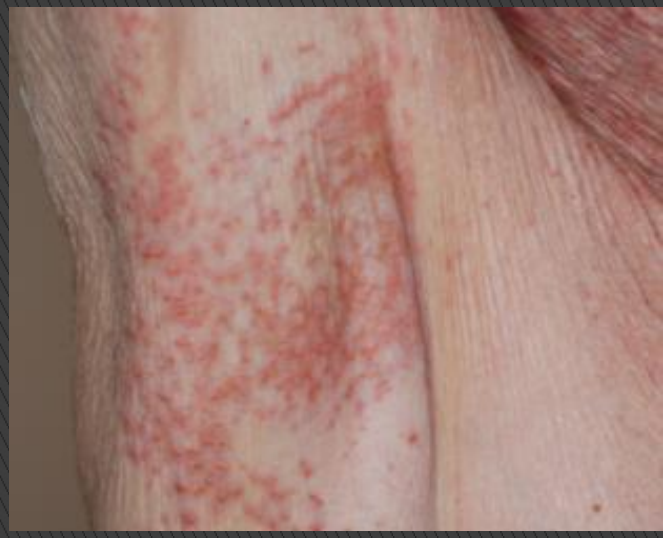
Journal of Clinical Oncology, Vol 29, No 12 (April 20), 2011: pp e340-e341

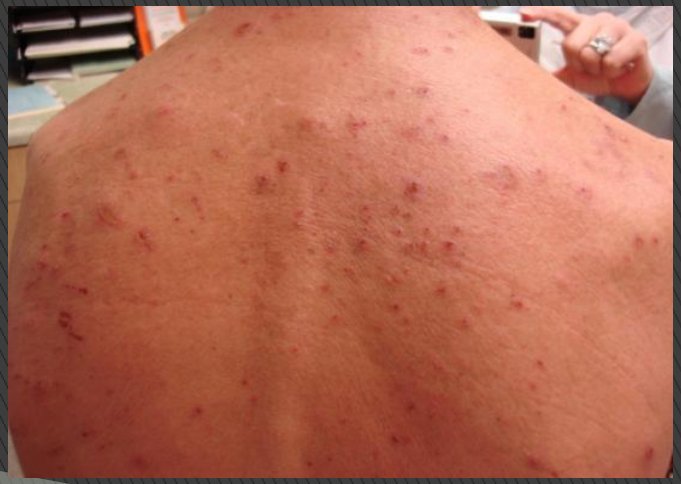
J Support Oncol. 2010 Jul (8) 4: 149-161

Xerosis,Pruritis

- 50% to 80%, xerosis presents within 2–3 weeks, followed by fissures at wk5
- Miniaturized eccrine sweat glands and compact stratum corneum
- Decreased QoL, Sleep deprivation
- Scratching and secondary infections

Xerotic Dermatitis





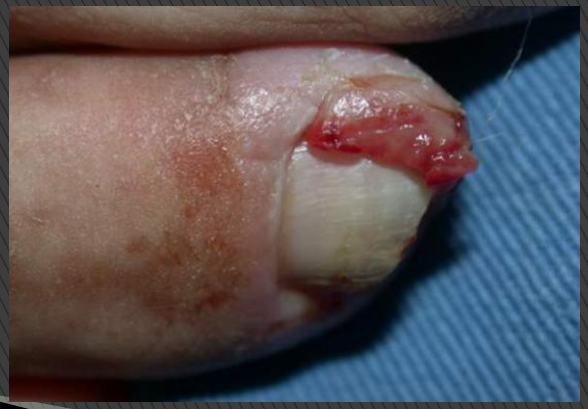
Lacouture ME, et al. Br J Dermatol. 2006;155:852-854. Mitchell EP, et al. Oncology (Williston Park). 2007;21(11 suppl 5):4-9. Osio A, et al. Br J Dermatol. 2009;161:515-521.

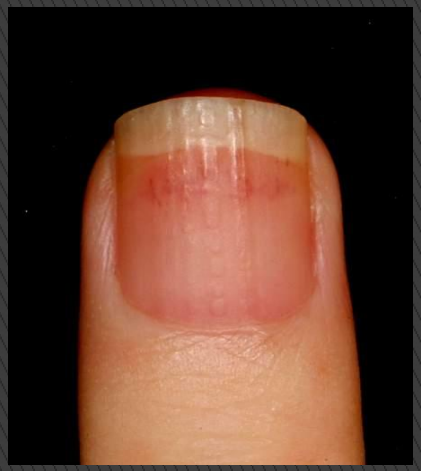
CTCAE 4.03 Grading

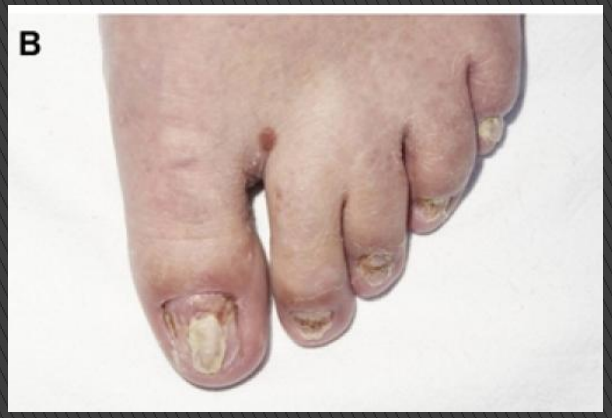
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation.					
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	-
Definition: A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture.					

Nail and nailfold changes

- Appears since wk5-8
- Panitumumab 24%, cetuximab and geftinib10-15%, <1% of lapatinib
- Paronychia and granuloma-like tissue
  - Inflict significant pain and affect activities of daily living
- Nail loss or nail ridging
- Subungual splitter hemorrhage





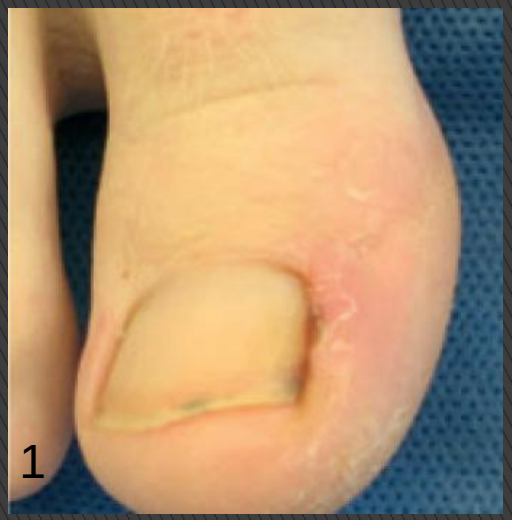


BMJ Case Rep. 2011

Lacouture Me et al. Curr Opin Oncol 2011, 23: 343-351

CTCAE 4.03 Grading

DISORDER	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Paronychia *Definition:* 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 (eg, antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self-care ADL		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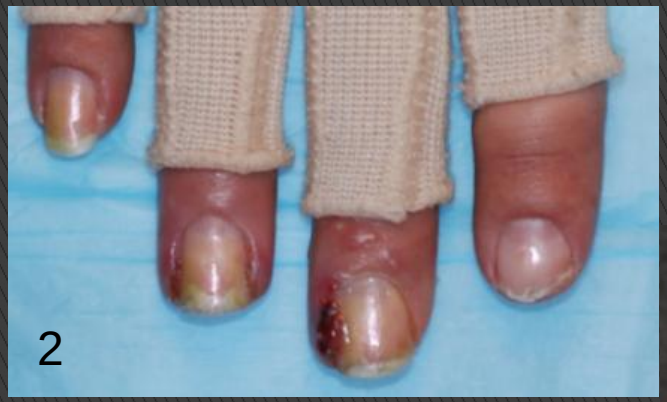
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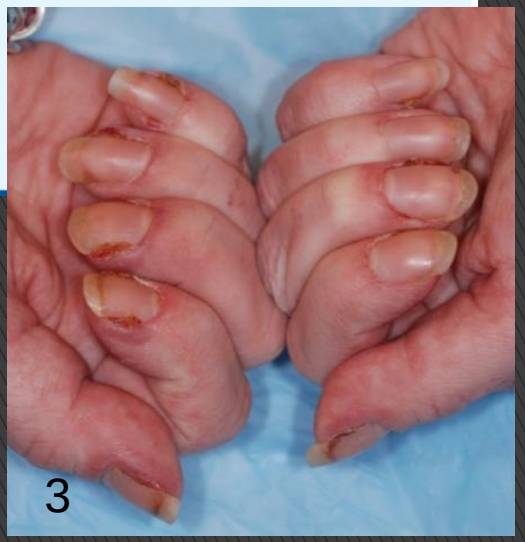
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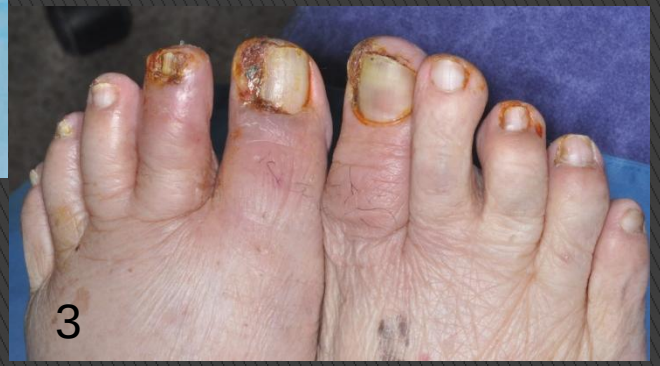
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Lacouture ME, et al. Br J Dermatol. 2006;155:852-854. Mitchell EP, et al. Oncology (Williston Park). 2007;21(11 suppl 5):4-9. Osio A, et al. Br J Dermatol. 2009;161:515-521. Manousaridis I etal. JEADV 2013, 27, 11–18

Hair Changes

- Pts receiving therapy > 2 months
  - Alopecia
  - Face: hair curling and hirsutism
  - Eyelash trichomegaly, trichiasis

Lacouture ME, et al. Br J Dermatol. 2006;155:852-854. Roe E, et al. J Am Acad Dermatol. 2006;55: 429-437. Vano-Galvan S, et al. J Am Acad Dermatol. 2010;62:531-533. Kerob D, et al. Arch Dermatol. 2006;142:1656-1657. Foerster CG, et al. Cornea. 2008;27:612-614.

CTCAE 4.03 Grading

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Alopecia	Hair loss of <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	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual at a given age and body location.					
Hypertrichosis	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/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: 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.					
Hirsutism	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	-	-	-
Definition: 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, moustache, chest, abdomen)					

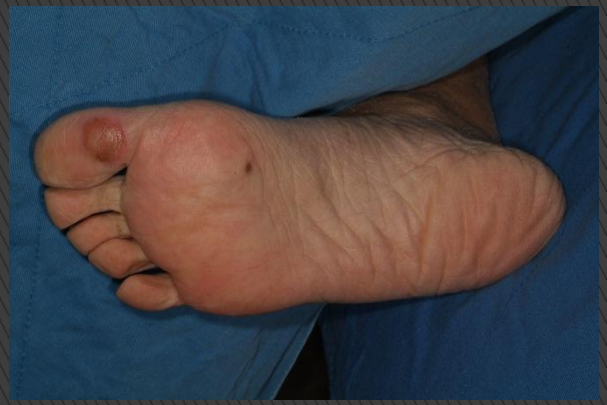
Cutaneous complications of targeted drug therapies

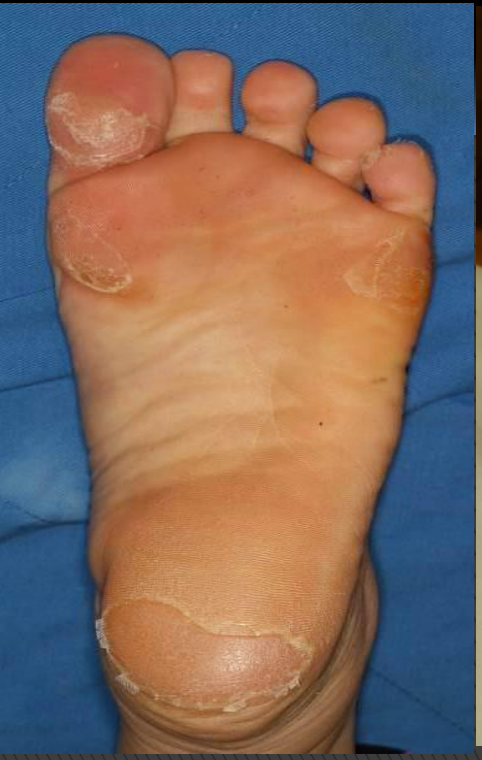
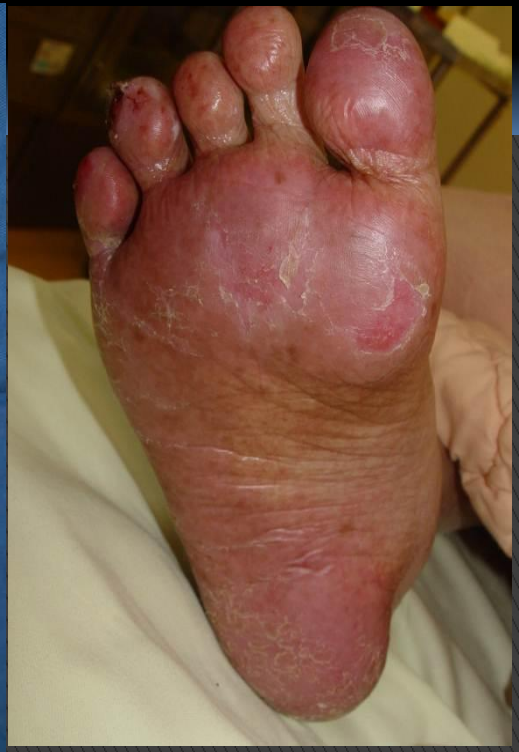
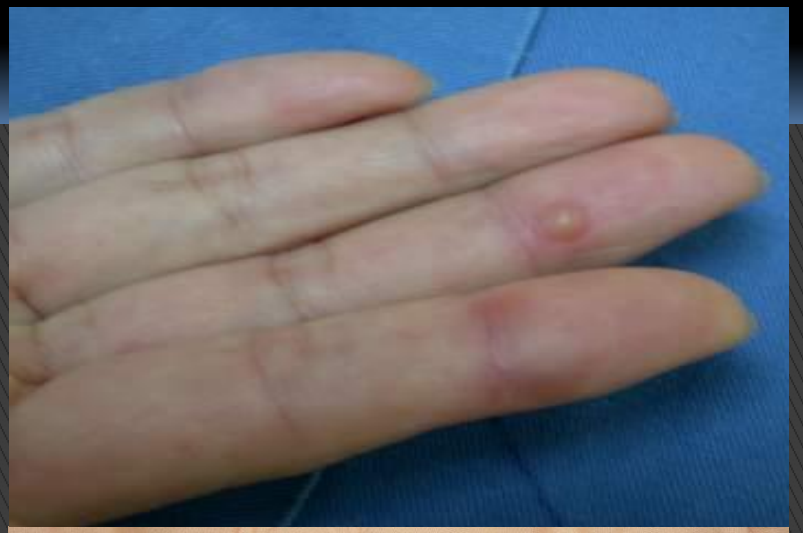
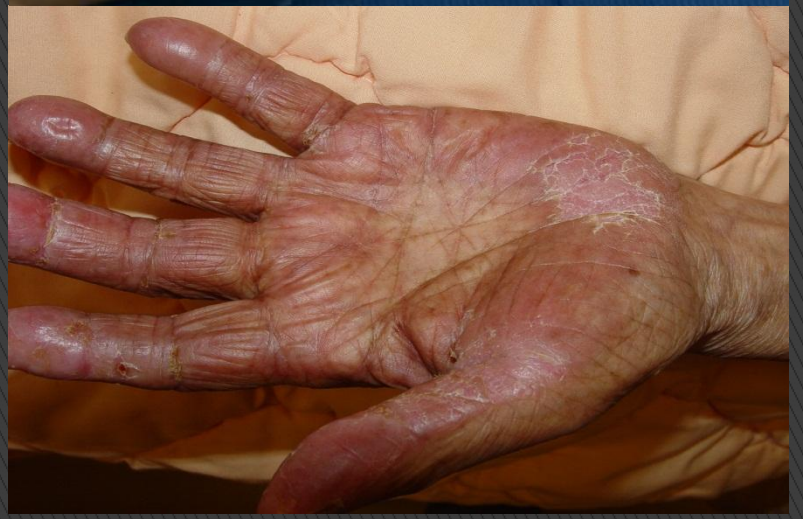
Molecular target(s)	Agent	Class	FDA-approved indication	Cutaneous side effects
VEGFR PDGFR KIT	Pazopanib (Votrient)	TKI	RCC, soft-tissue sarcoma	• Hand/foot skin reactions • Redness and flaking on scalp and eyebrows • Warm, burning sensation on face along with redness • Xerosis, fissures and pruritus • Hair loss on scalp • Pazopanib, Sunitinib: gray hair
VEGFR PDGFR KIT RAF	Sorafenib (Nexavar)	TKI/STKI	HCC, RCC	
VEGFR PDGFR KIT RET	Sunitinib (Sutent)	TKI	GIST, RCC, Panceratic neuroendocrine tumor	
VEGFR PEGFR TIE2 KIT RET BRAF	Regorafenib (Stivarga)	TKI	metastatic CRC, GIST	

Adopted from Cancer.net & AJR Am J Roentgenol. 2013 March ; 200(3): 475–483.

Hand-Foot skin reactions

- Palmoplantar erythrodysesthesia syndrome
  - Dysesthesia and tingling sensation of palms and soles
- Well-defined symmetric swelling and erythema; may also affect the lateral sides or the periungual zones
- Dry and/or cracked skin
- Callous-like blisters , usually not containing fluid
- Dose dependent
- 24 hours to 10 months
  - median times: 6 to 126 days



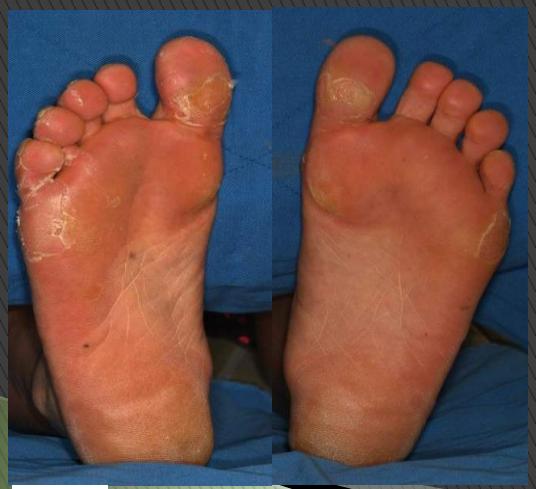





- Multiple kinase inhibitor ➔
  more localized tender and hyperkeratosis, blisters formation
  Soles>Palms
- Chemotherapy(fuorouracil, capecitabine, anddoxorubicin)➔
  diffuse and symmetric erythema
  palm>sole

J Support Oncol. 2010 Jul (8) 4: 149-161

CTCAE 4.03 Grading

DISORDER	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Palmar-plantar erythrodysesthesia syndrome[a] *Definition:* a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet	Minimal skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis) without pain	Skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL		



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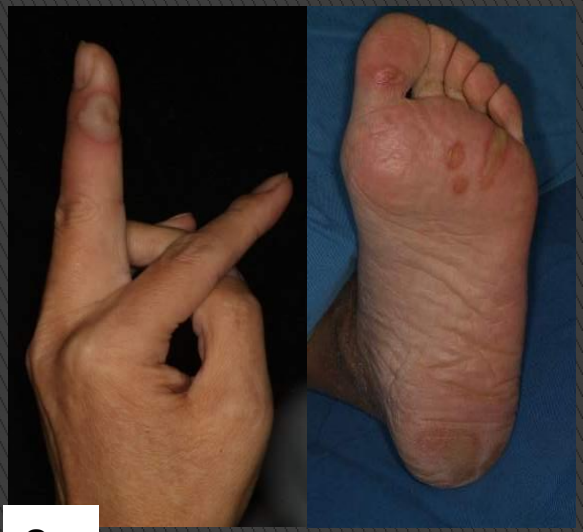

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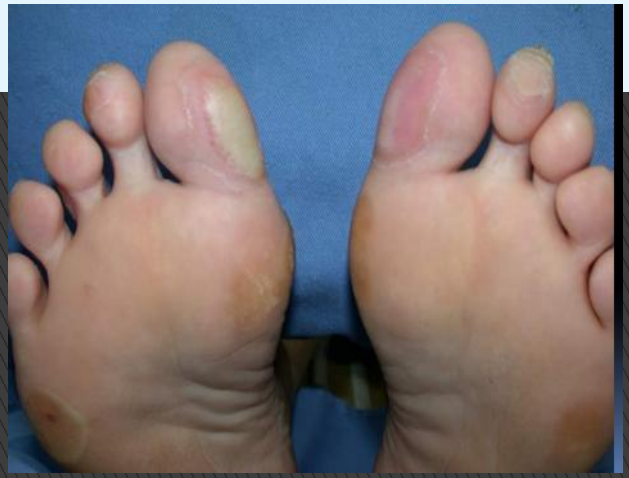
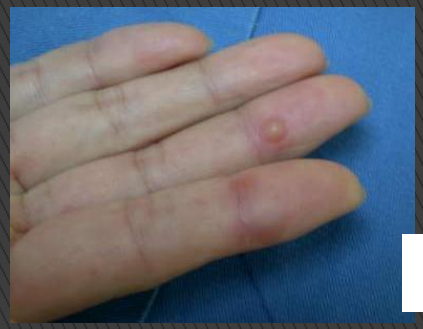




3

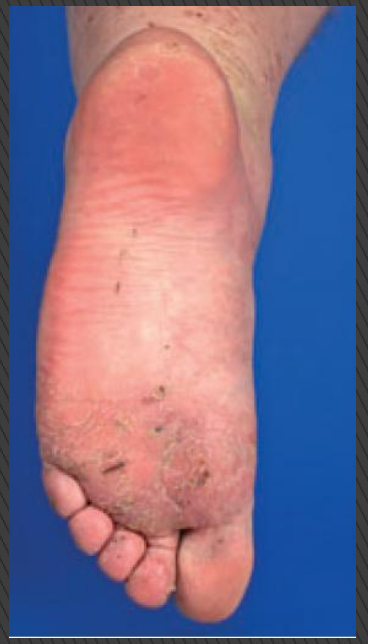
Cutaneous complications of targeted drug therapies

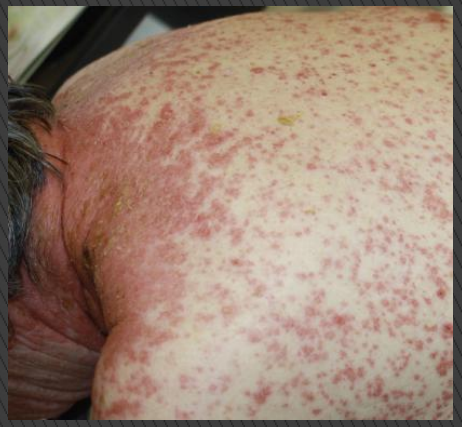
Molecular target(s)	Agent	Class	FDA-approved indication	Cutaneous side effects
RAF	Vemurafenib (Zelboraf) Debrafenib (Tafinlar)	STKI	Melanoma	• Papulopustular rash • Hand/foot skin reactions • Xerosis, fissures and pruritus • Paronychia • Hyperkeratosis • KA, SCC
mTOR	Everolimus (Afinitor) Temsirolimus (Torisel)	STKI	RCC Breast cancer, Pancreatic neuroendocrine tumor, RCC	• Stomatitis/ aphthous ulceration • Papulopustular rash
CTLA	Ipilimumab (Yervoy)	mAb	Melanoma	• Bumpy red rash • Itching • Vitiligo and gray hair

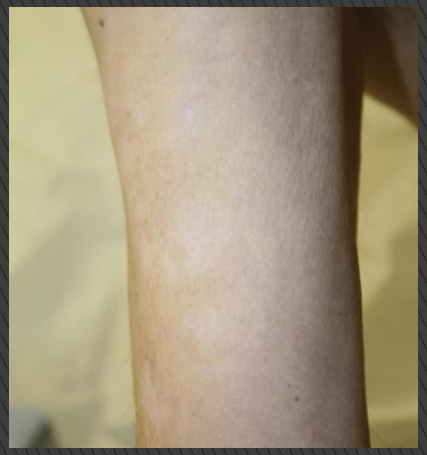
- Adopted from Cancer.net & AJR Am J Roentgenol. 2013 March ; 200(3): 475–483.

Other cutaneous side effects

- Hair depigmentation, hair graying
- Vitiligo
- Hyperkeratosis
- Keraotacanthoma and squamous cell carcinoma
  - 15–30% of patients treated with BRAF inhibitors





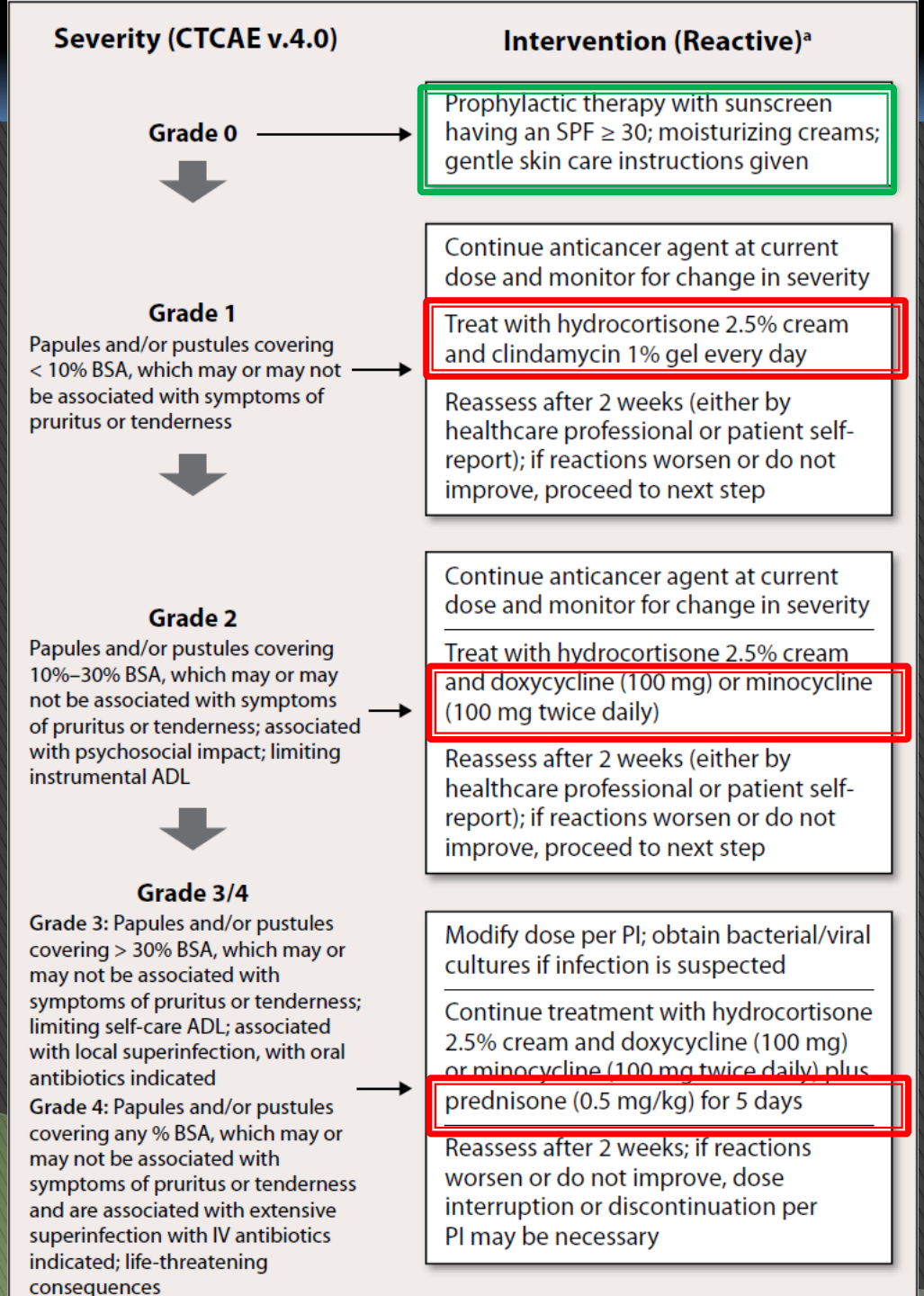


ASCO POST 2013, Volume 4, Issue 16
Manousaridis I etal. JEADV 2013, 27, 11–18
Su F. et al., *NEJM* 2011; 366: 207-15

Management

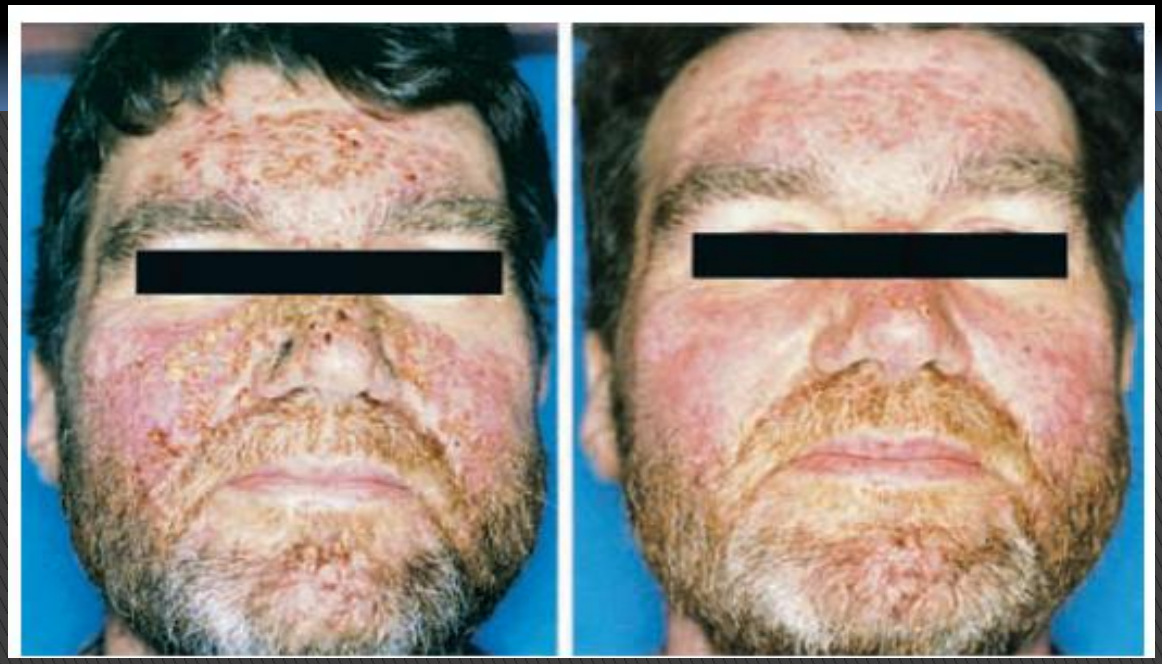
- Do not forget the patient education

Papulopustular rash recommendations



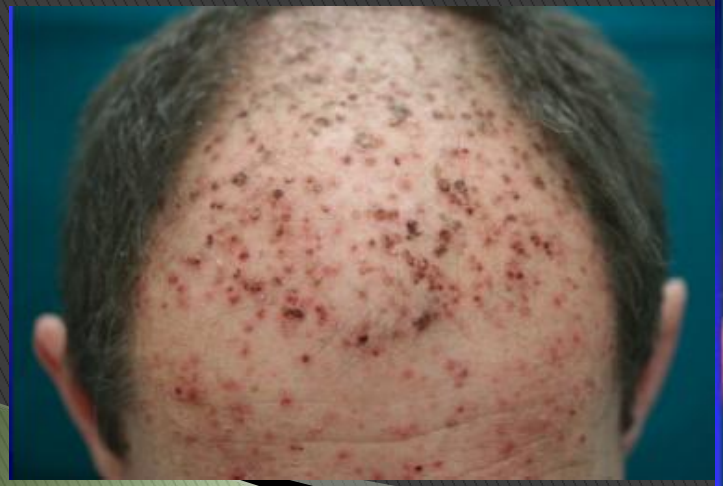
DO NOT USE over the counter acne medications that contain benzoyl peroxide (drying)

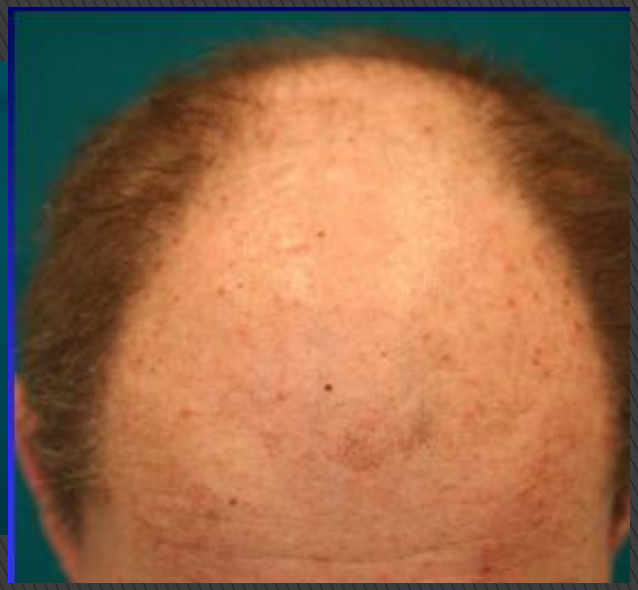
J Support Oncol. 2010 Jul (8) 4: 149-161



right side face: hydrocortison
left side face: tazarotene

Scope A. et al. J Clin Oncol 2007; 25:5390-5396





Two weeks of
vitamine K cream

Ocvirk J, Rebersek M. WCGIC 2009 Poster PD0021

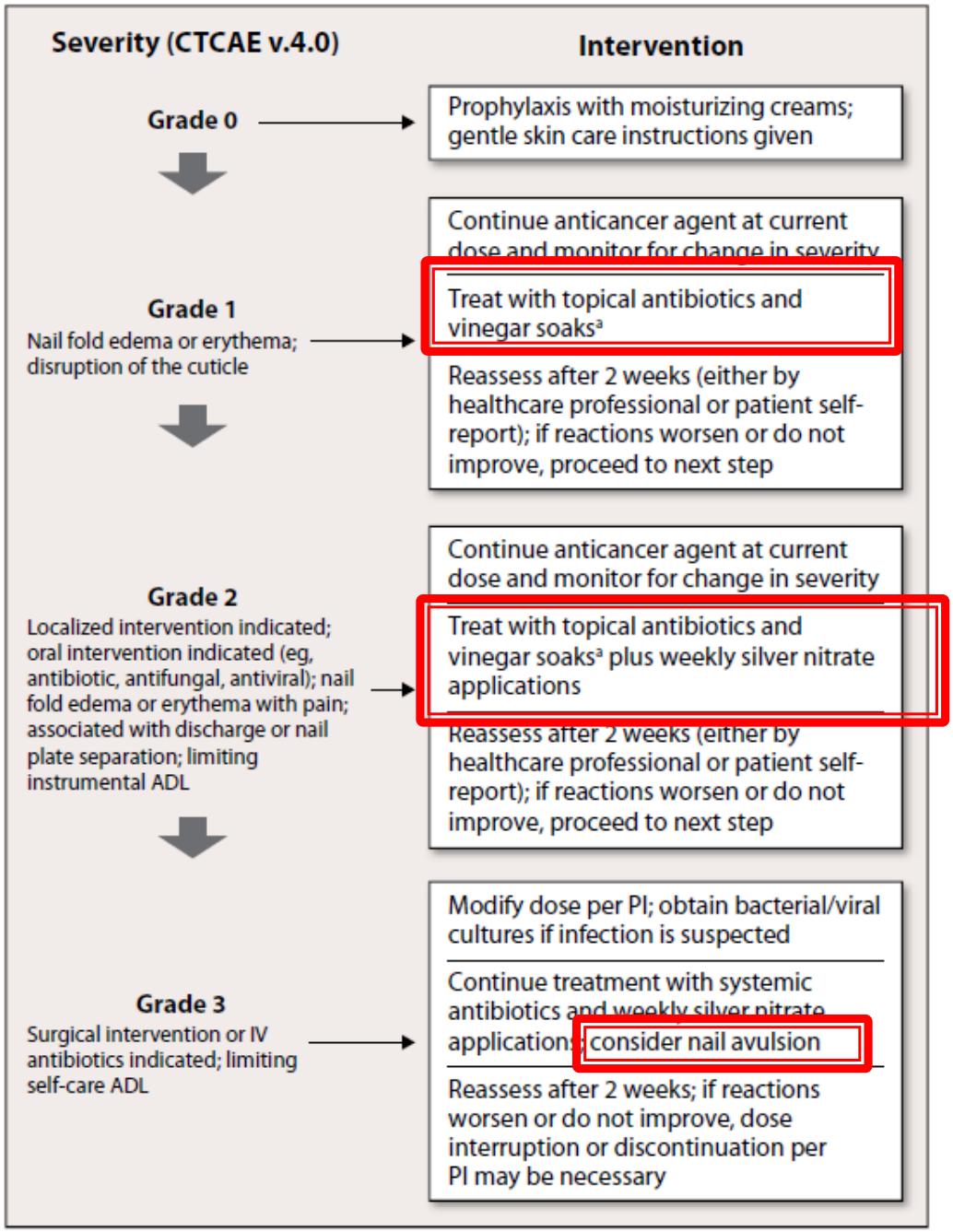


Figure 10 Treatment Algorithm for Paronychia

Nail changes recommendations

- Petrolatum as protection
- Wear comfortable shoes
- Avoid prolonged or frequent water immersion

J Support Oncol. 2010 Jul (8) 4: 149-161

Pruritus Recommendations

Preventive	Recommended	Level of Evidence	Recommend-ation Grades	Comments
Topical	Gentle skin care instructions	IV*†	D	Consensus of experts
Systemic		IV*†	D	Consensus of experts
Treatment	Recommended	Level of Evidence	Recommend-ation Grades	Comments
Topical	▪ Menthol 0.5% pramoxine, 1% doxepin ▪ Medium- to high-potency steroids (triamcinolone acetonide 0.025%;, desonide 0.05%, fluticasone propionate 0.05%, alclometasone 0.05%)	III†	B	Treat underlying condition first (rash, xerosis)
Systemic	Antihistamines†	I‡	A	Nonsedating first; some may need adjustment for renal impairment
Systemic	Gabapentin/pregabalin*	V*†	D	Recommended as second-line treatment only if antihistamines fail
Systemic	Doxepin	V*	D	

Lacouture ME, et al. Support Care Cancer. 2011;19:1079-1095.

*EGFR inhibitor study.
†Non–EGFR inhibitor noncancer treatment study.
‡Non-EGFR inhibitor cancer treatment study.

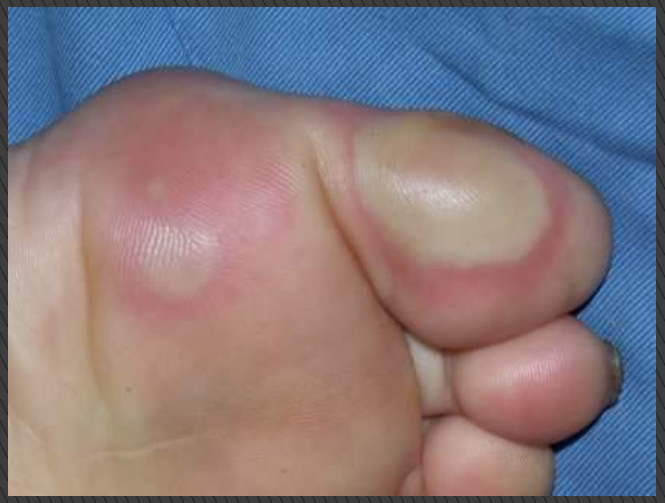
Hair Changes Recommendations

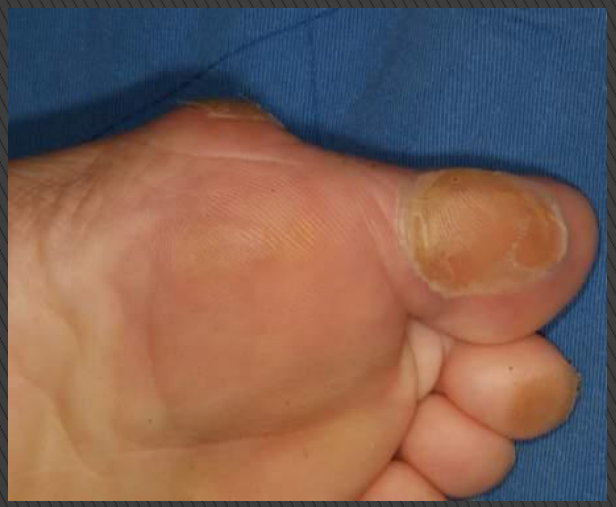
	Recommended	Level of Evidence	Recommend-ation Grades	Comments
Preventive hair loss				
Topical	??			
Systemic	??			
Treatment for hair loss				
Topical	▪ **Nonscarring** • **Minoxidil 2%, 5% BID** ▪ **Scarring** • **Class 1 steroid lotion, shampoo, or foam** • **Antibiotic lotion**	**I*/II/III/IV†**	**B/D**	**Consensus of experts**
Preventive increased hair	Patient education and support	IV	B	Consensus of experts
Treatment for increased hair				
Facial hypertrichosis	▪ **Eflornithine (DFMO)** ▪ **Lasers**	IV,† II*	B	Consensus of experts
Eyelash trichomegaly	Eyelash trimmings regularly	IV	B	

*Non–EGFR inhibitor noncancer treatment study.
†EGFR inhibitor study.

Lacouture ME, et al. Support Care Cancer. 2011;19:1079-1095.

Severity (CTCAE v.4.0)	Intervention
Grade 0	Prophylaxis with ammonium lactate 12% cream twice daily or heavy moisturizer (eg, petroleum jelly) twice daily
Grade 1 Minimal skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis) without pain	Continue treatment at current dose and monitor for change in severity Treat with urea 20% cream twice daily and clobetasol 0.05% cream once daily Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve, proceed to next step
Grade 2 Skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Continue treatment at current dose and monitor for change in severity Treat with urea 20% cream twice daily and clobetasol 0.05% cream once daily and control pain with NSAIDs/GABA agonists/narcotics Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve, proceed to next step
Grade 3 Severe skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL	Interrupt treatment until severity decreases to grades 0–1 Continue treatment with clobetasol 0.05% cream twice daily and control pain with NSAIDs/GABA agonists/narcotics Reassess after 2 weeks; if reactions worsen or do not improve, dose interruption or discontinuation per PI may be necessary





Skin care for HFSR

Skin care products	Product information
Cetaphil skin cleanser, Aveeno shower gel	Non-deodorant, non-fragrance products
Udderly Smooth, Gold Bond, Aveeno	Thicker products with more intense moisturizing properties than basic lotions. Anti-itch formulations are available.
Norwegian Formula: Soothing Relief Anti-Itch Moisturizer by Neutrogena	Contains dimethicone 1%, camphor 0.1%, and lidocaine
Norwegian Formula: Foot Cream by Neutrogena	Contains ceterayl alcohol, dimethicone, menthol, and urea
Bag Balm	May provide "cooling" effect from eucalyptus
Eucerin Cream	Best used at night due to greasy formulation
Eucerin Dry Skin Therapy	Contains trea and alpha hydroxy acid
Aquaphor Healing Ointment	Petrolatum 41%
Kerasal	Salicylic acid 5% exfoliates and softens skin; urea 10% moisturizes skin

Risk Factors??

- ✓ Drug dosage

Patient factors???

- advanced age
- female sex
- performance status
- total body irradiation
- ethnic ,genetic
- Asians: 45%~55%

From management to prevention

- What else we can do?

STEPP Study: Preemptive vs Reactive Skin Toxicity Treatment in Metastatic CRC

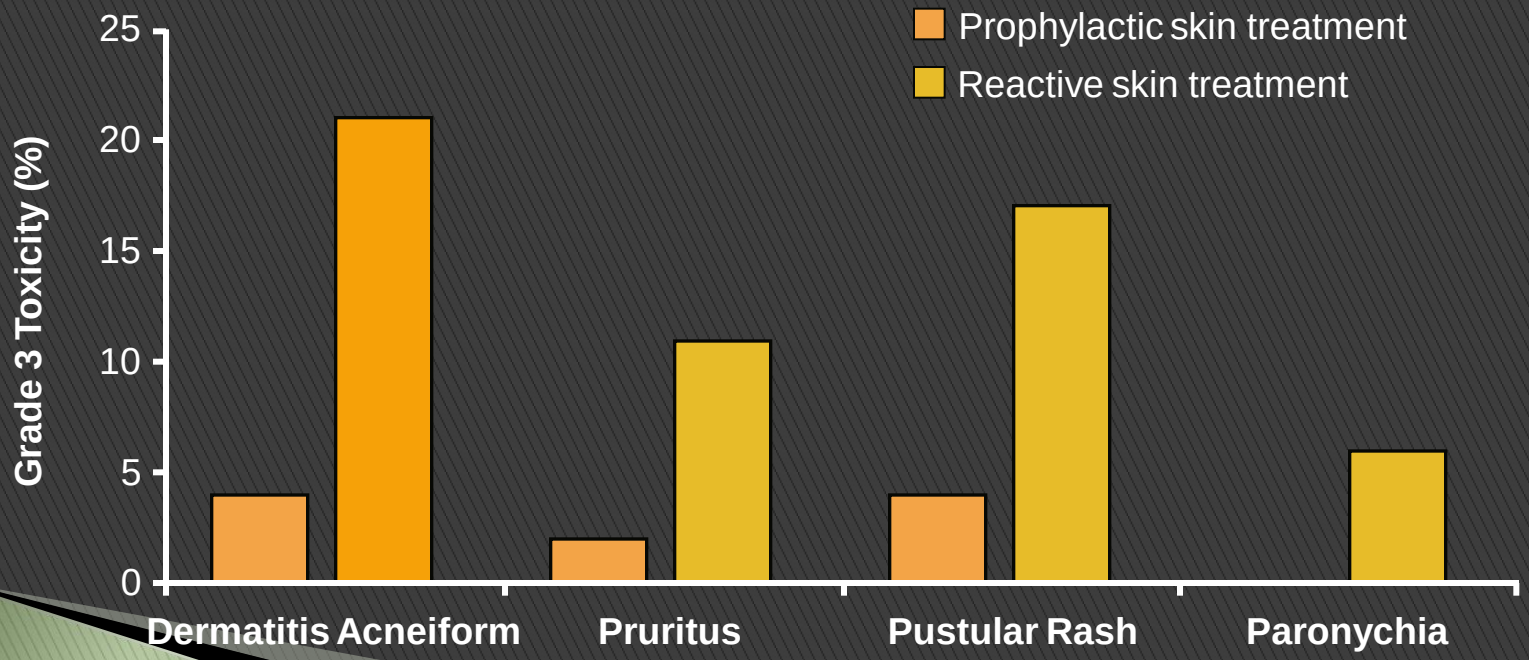
- Open-lable phase II study
- Prophylactic skin treatment regimen administered Wks 1-6 (beginning Day 1)
  - Skin moisturizer
  - Sunscreen (PABA free, SPF $\geq$ 15, UVA/UVB protection)
  - Topical steroid (1% hydrocortisone cream)
  - Doxycycline 100 mg BID
- Per investigator discretion, reactive skin treatment administered anytime during Wks 1-6

Lacouture ME, et al. J Clin Oncol. 2010;28:1351-1357.

STEPP: Dermatologic Toxicities

	Prophylactic (n = 48)	Reactive (n = 47)
Patients with grade 2 or higher skin toxicity, n (%)	14 (29)	29 (62)
OR (95% CI)	0.03 (0.1-0.6)	

Skin side effects can be reduced with prophylactic treatment



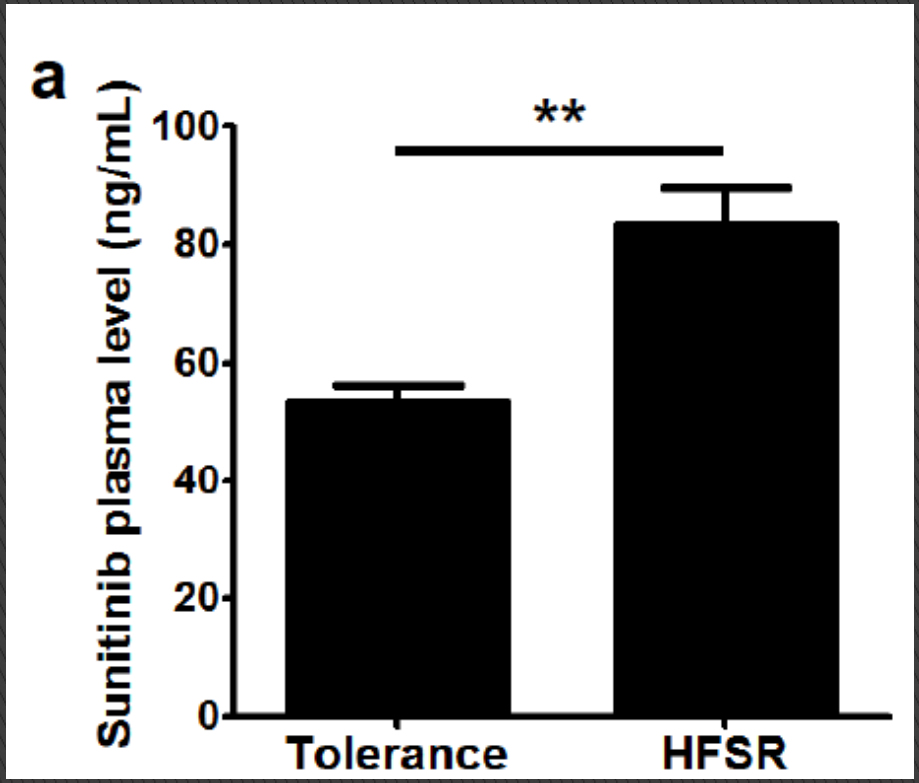
Lacouture ME, et al. J Clin Oncol. 2010;28:1351-1357.

Pathomechanism of Multi-targeted Tyrosine Kinase Inhibitor-induced Hand-foot Skin Reaction

Fas/Fas Ligand Mediates Keratinocyte Death in Sunitinib-Induced Hand-Foot Skin Reaction

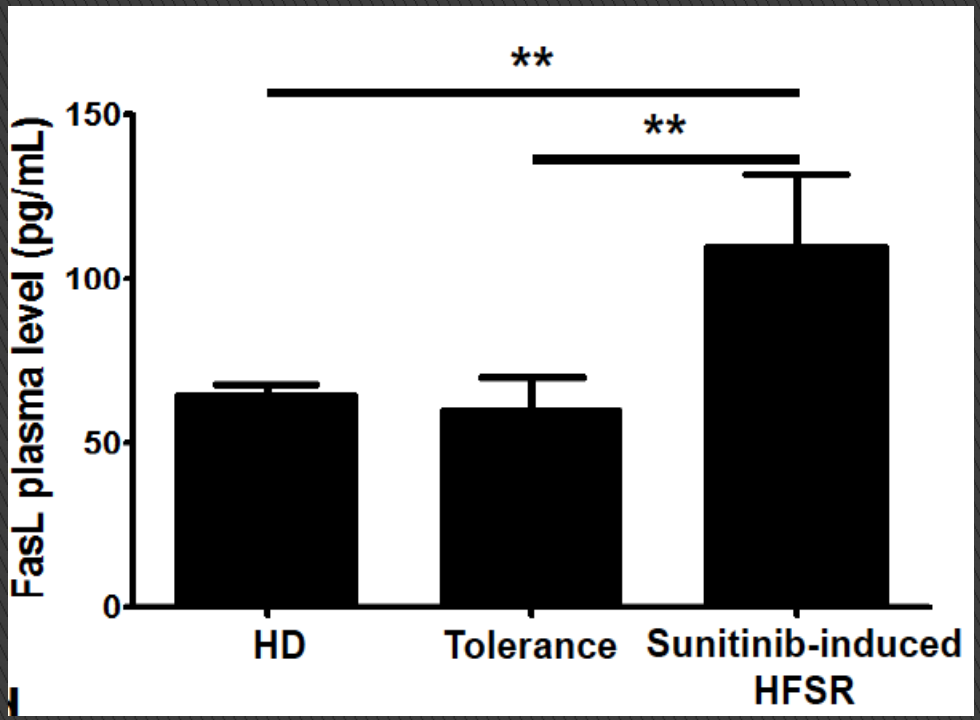
Chun-Nan Yeh[1,6], Wen-Hung Chung[2,6], Shih-Chi Su[2], Yen-Yang Chen[3], Chi-Tung Cheng[1], Yen-Ling Lin[4], Wan-Chun Chang[4], Rosaline Chung-Yee Hui[2], Kun-Chun Chiang[1], Tsung-Wen Chen[1], Yi-Yin Jan[1], Chien-Wei Chen[4], Ting-Jui Chen[4,5], Chih-Hsun Yang[2] and Shuen-lu Hung[4]

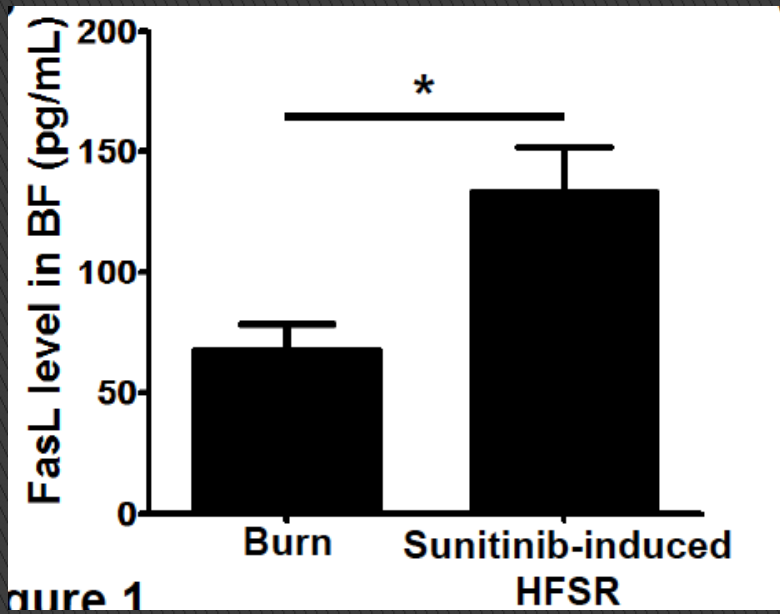
- 53 sunitinib-treated patients
  - 23 HFSR cases
  - 30 tolerant controls
- Elevated plasma levels of sunitinib in patients with HFSR



J Invest Dermatol doi:10.1038/jid.2014.218; accepted article preview online May 6, 2014

Elevated Fas-L levels in the Plasma and blister fluids of HFSR patients





gure 1

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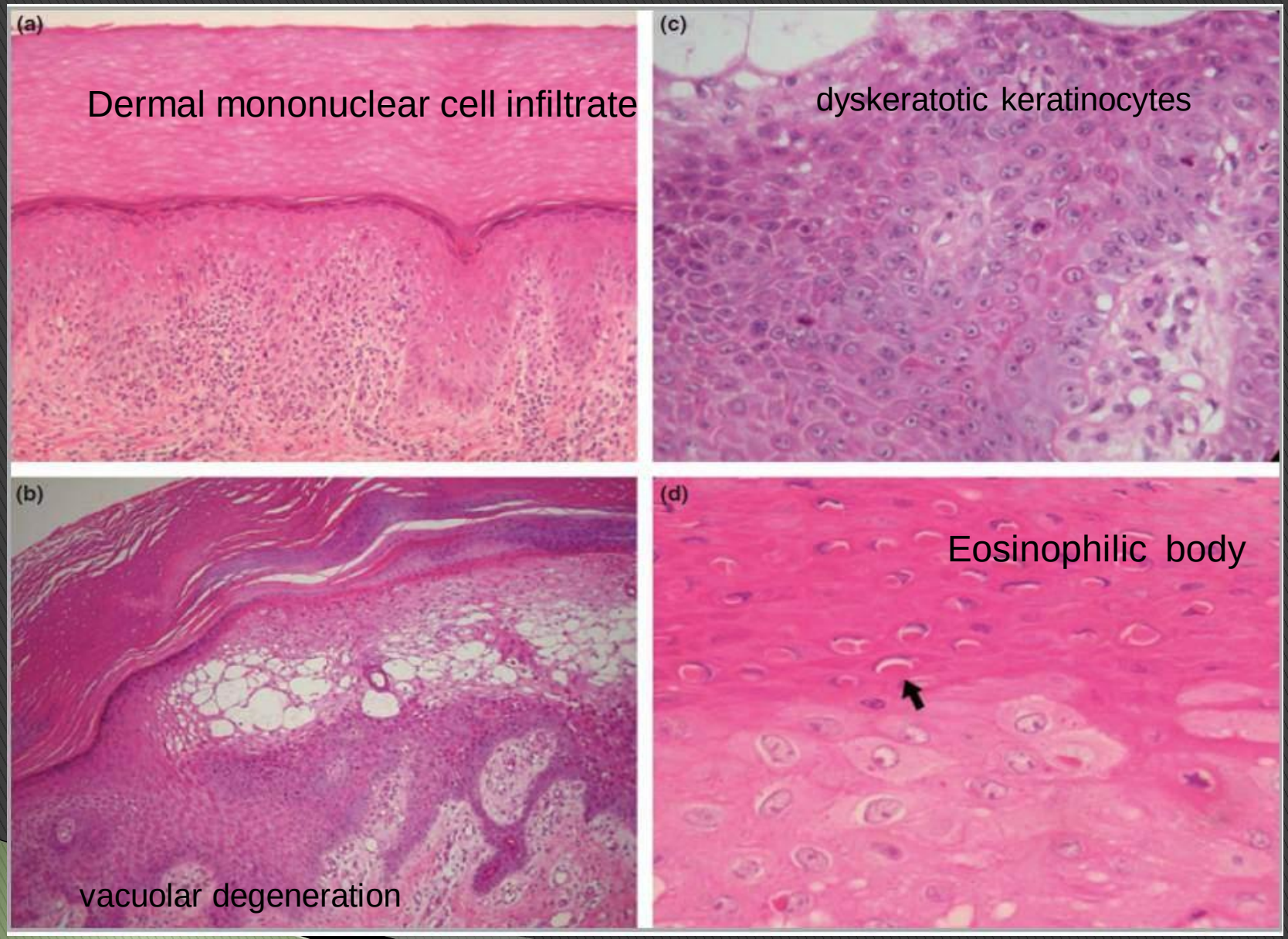
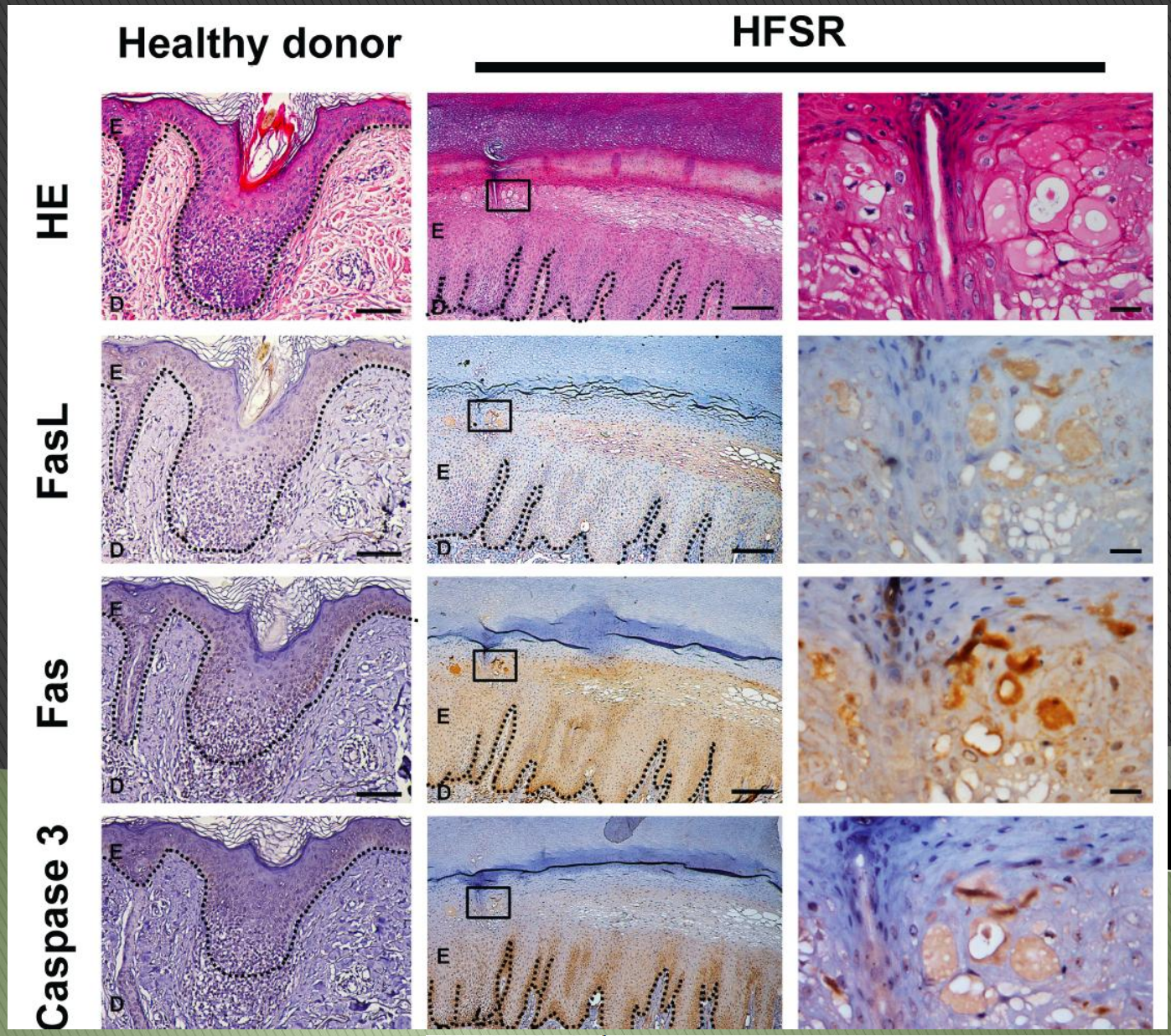
HISTOPATHOLOGY



J Invest Dermatol doi:10.1038/jid.2014.218; accepted article preview online May 6, 2014

Increased expression of FasL, Fas and caspase-3 in HFSR lesions



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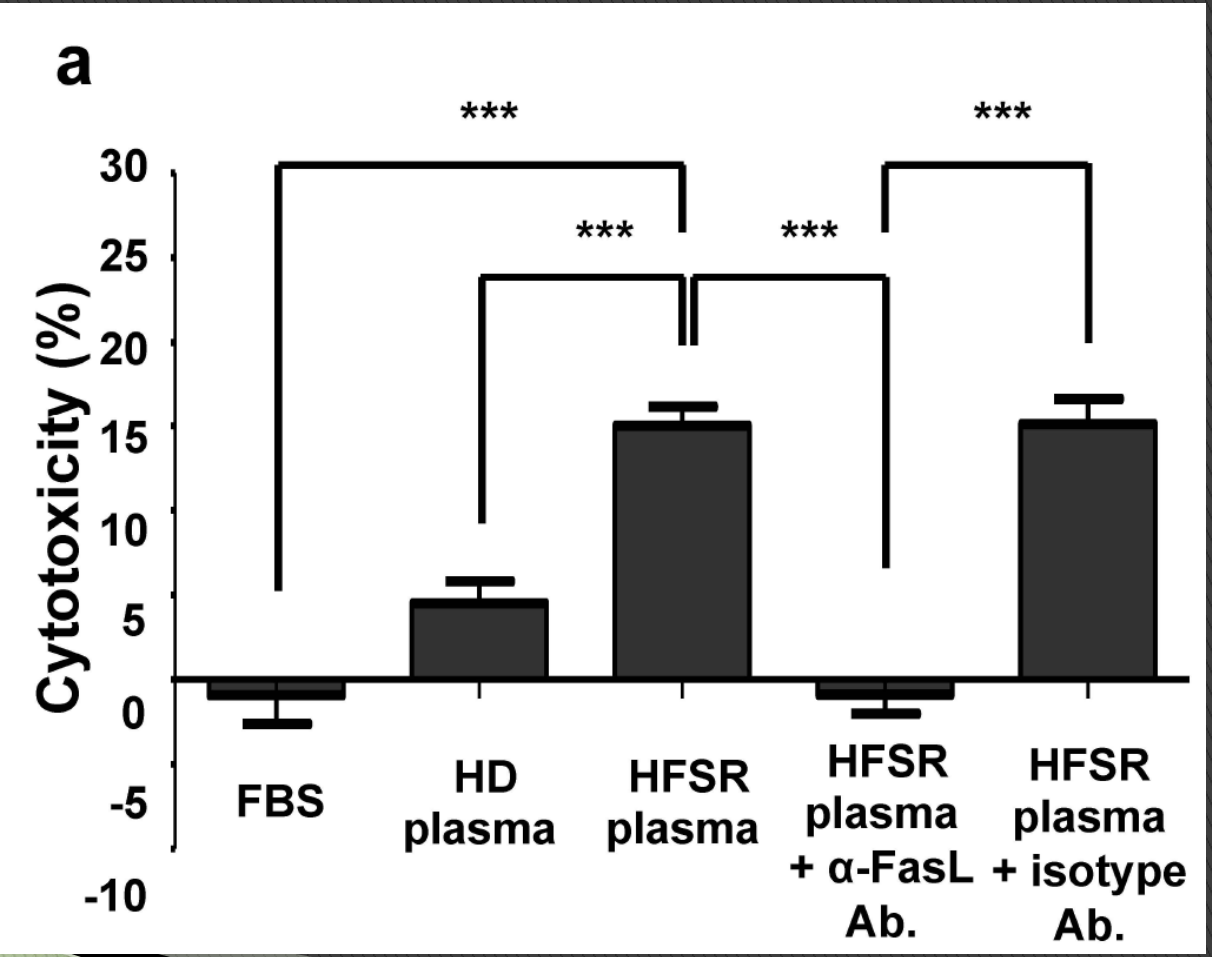
Fas-L mediates the cytotoxicity of HFSR plasma to keratinocytes

Anti-FasL antibody block keratinocytes apoptosis



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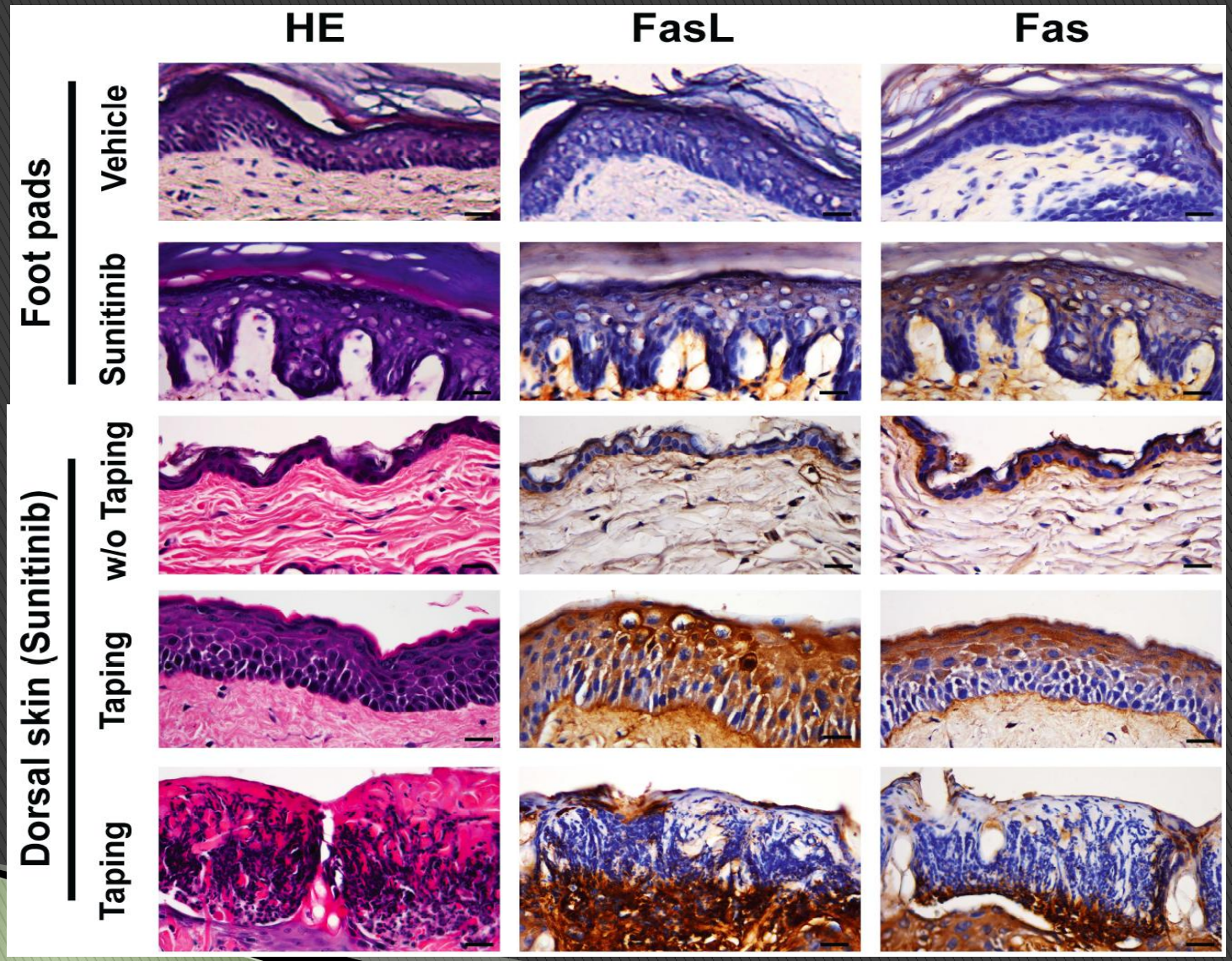
Sunitinib increased the expression of Fas/FasL in mice keratinocytes



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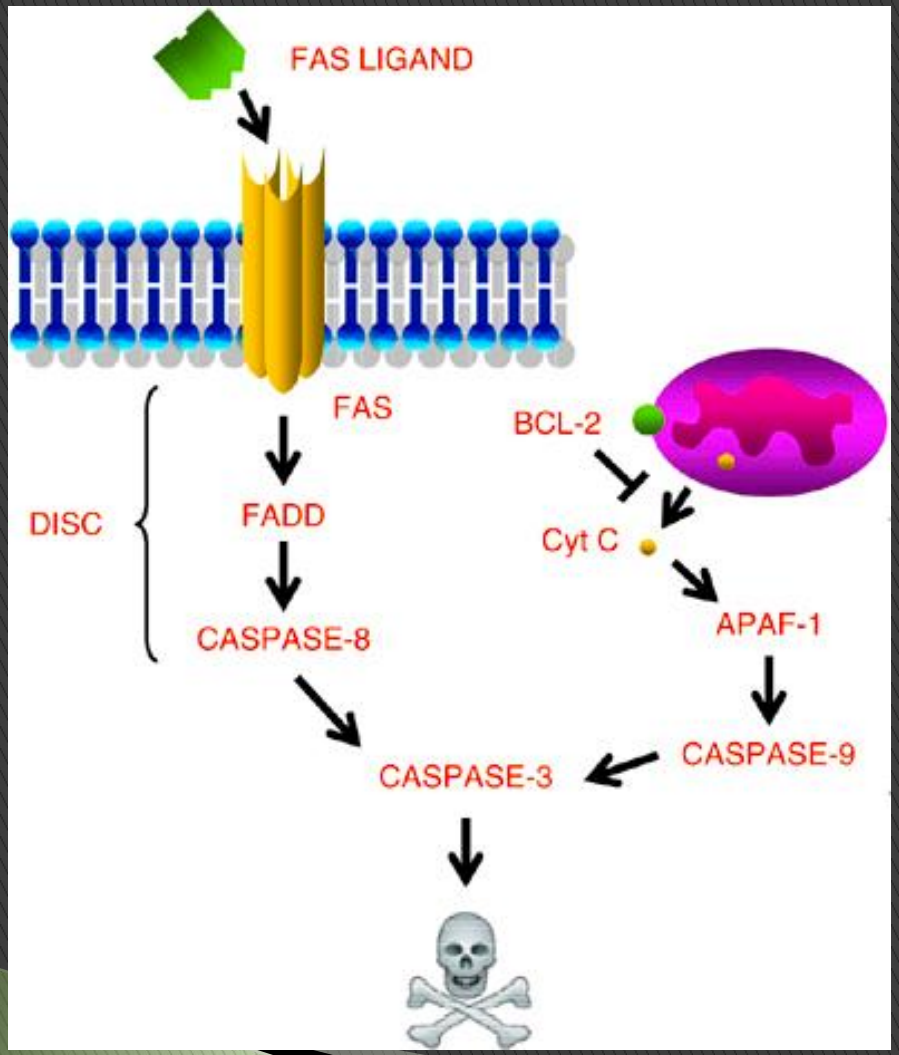

Increased plasma levels of FasL and overexpression of Fas in keratinocyctes is found in HFSR patients and animal model

Fas/FasL interaction mediates keratinocyte death in HFSR

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Conclusion

- Goal of therapy: alleviate patient discomfort, improve quality of life, minimize treatment interruptions
- Proactive approach help to limit the incidence of severe symptoms
- The skin toxicities are manageable and reversible
- Characterization of dermatologic toxicities will increase in importance
  - Adjuvant setting
  - Dose escalation and combination studies
  - Longer survival

Thank you for listening!

For any comment or question:

lanakao@cgmh.org.tw