UniversitätsKlinikum Heidelberg

# Preventing and managing skin toxicities

Karin Jordan

# Many aspects of skin toxicity

Radiation recall

Edema

Rash

Pruritus

Photosensitization

Nails

Hand-Foot-Syndrom

Alopecia

Hyperpigmentation

# How to prevent, how to treat?
# - Guidelines-

- ESMO ☹
- ASCO ☹
- MASCC 2011 ☺
- S3 Guideline 2016 ☺

MASCC: Lacatoure, J Support Care Cancer 2016

S3 Guideline "Supportive Therapy“: Karin Jordan Guideline coordinator, Franziska Jahn Guideline secretary 2016, AWMF Register-No: 032-054OL

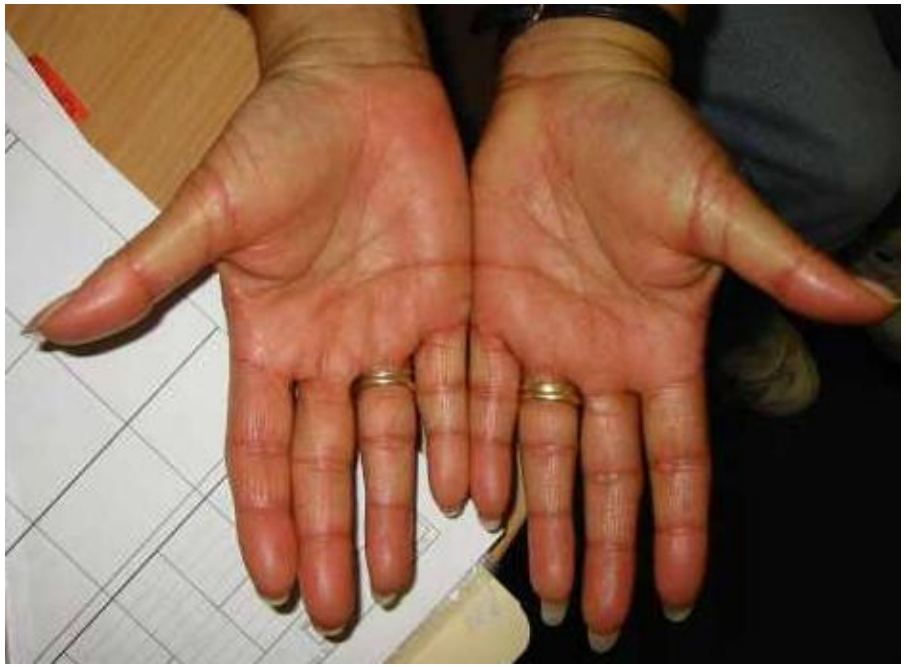
# S3 Guideline Supportive Care in Cancer Patients

- Evidence based Recommendations- Grades

| Grade of recommendation | Description | Wording |
|---|---|---|
| A | Strongly recommended | must |
| B | Recommended | should |
| 0 | Neither recommended nor not recommended | can |

- Evidence based Statements
- Expert Consensus

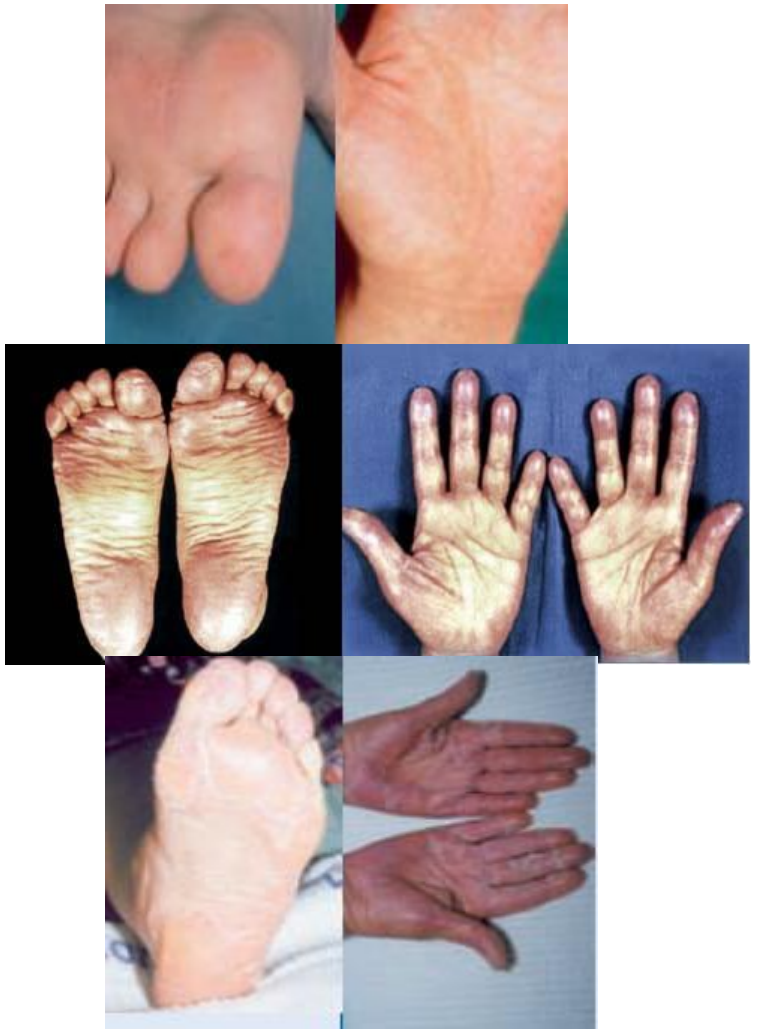
S3 Guideline Supportive Care in Cancer Patients:
Karin Jordan Guideline coordinator, Franziska Jahn Guideline secretary
2016, AWMF Register-No: 032-054OL



# HAND-FOOT- SYNDROME

# Hand-Foot-Syndrome: Classification

| Grade | NCI-CTC Version 3.0 |
|---|---|
| 1 | Slightly marked, painless erythema |
| 2 | Erythematous skin lesions (scaling of the skin, blisters, bleeding, swelling) or pain **without functional impairment** |
| 3 | Ulcerative dermatitis or skin changes associated with pain and **functional impairment** |



# Hand-Foot-Syndrome Incidence

| Drug | CTC: alle Grade | ≥ Grad 3 |
|---|---|---|
| Capecitabine | 50-60 % | 10-17 % |
| Sorafenib | 34 % | 9 % |
| Sunitinib | 19 % | 6 % |
| Regorafenib | 61 % | 20 % |
| 5-Fluorouracil (continious) | 35 % | 7 % |

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# Prevention of Hand-Foot-Syndrom??

J Clin Oncol. 2010 Aug 20;28(24):3824-9. doi: 10.1200/JCO.2010.29.1807. Epub 2010 Jul 12.

**Pyridoxine is not effective to prevent hand-foot syndrome associated with capecitabine therapy: results of a randomized, double-blind, placebo-controlled study.**

Kang YK[1], Lee SS, Yoon DH, Lee SY, Chun YJ, Kim MS, Ryu MH, Chang HM, Lee JL, Kim TW.

Author information

**Abstract**

**PURPOSE:** To determine whether concurrent pyridoxine therapy can prevent the development of hand-foot syndrome (HFS) in patients being treated with capecitabine.

**METHODS:** Chemotherapy-naive patients with GI tract cancers scheduled for capecitabine-containing chemotherapy were randomly assigned to concurrent oral pyridoxine (200 mg/d) or placebo. Patients were stratified by chemotherapy regimen and monitored until development of National Cancer Institute Common Toxicity Criteria grade 2 or worse HFS or capecitabine-containing chemotherapy ended. Patients in the placebo group who developed grade 2 or worse HFS were randomly assigned again to receive pyridoxine or placebo in the next chemotherapy cycle to determine whether pyridoxine could improve HFS.

**RESULTS:** The median number of chemotherapy cycles to grade 2 or worse HFS was three in both groups. Grade 2 or worse HFS developed in 55 (30.6%) of 180 placebo-treated patients and in 57 (31.7%) of 180 pyridoxine patients. The cumulative dose of capecitabine to grade 2 or worse HFS was not different between the two groups (median not reached in either group; hazard ratio [HR] = 0.95; P = .788). Randomization of the 44 patients in the placebo group with grade 2 or worse HFS to placebo or pyridoxine for the next cycle resulted in no significant difference in the proportion showing improvement of HFS (42.9% v 47.8%; HR = 1.12; P = .94). By multivariate analysis, age > or = 56 years (HR = 1.768; 95% CI, 1.190 to 2.628; P = .005) was an independent risk factor for grade 2 or worse HFS, and combined use of docetaxel (HR = 2.046; 95% CI, 0.880 to 4.755; P = .096) was of borderline significance.

**CONCLUSION:** Pyridoxine is not effective in prevention of capecitabine-associated HFS.

+ new metaanalysis, JSCC 2014: **No effect of Pyridoxine**

Support Care Cancer. 2014 Jun;22(6):1585-93.

# Prevention ?

# Hand-Foot-Syndrome: Prophylaxis

**MUST: Treatment of hyperkeratoses / fungal infections ( A, LoE 5)**

**Pressure relief** (comfortable shoes, avoidance of friction, and heat) **( A, LoE 5)**

**SHOULD: Intensive skin care of hands and feet** (Urea hand and foot cream/ ointment, for example Eucerin® 10 %) **(B, LoE 1b)**

**CAN: Cooling hand and foot** during infusion with Docetaxel **(0, LoE 2b)**

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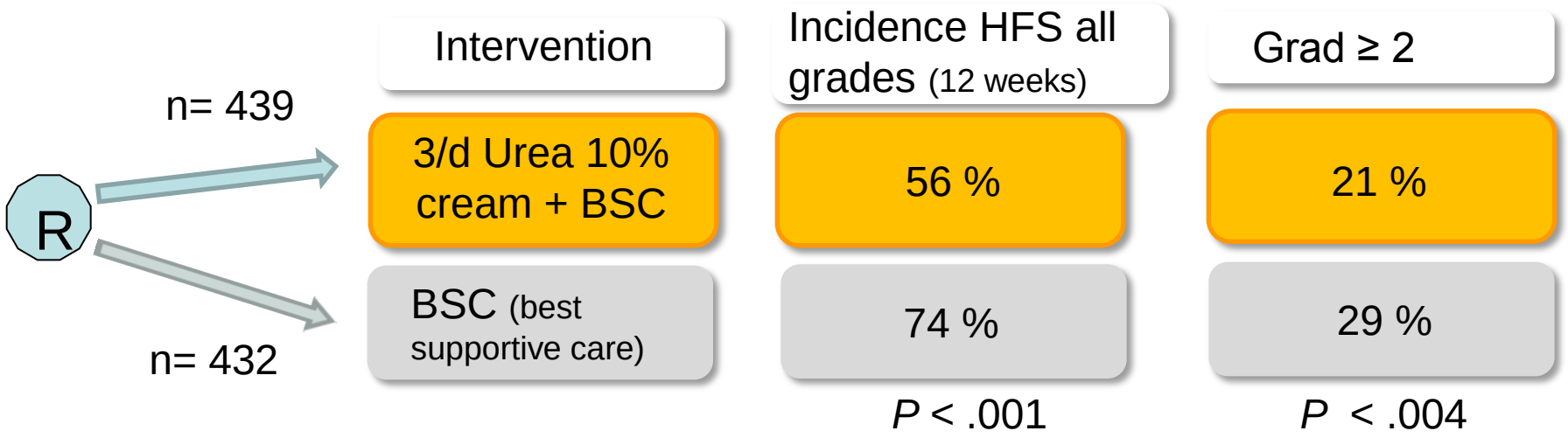
# Prevention of Hand-Foot-Syndrome (HFS) – Urea-containing cream

***Ren Z. et al., J Clin Oncol 2015***

Patients with mit hepatocallular carcinoma + Sorafenib




Conclusion:

10 % urea-containing cream significantly reduces the appearance of HFS

# Hand-Foot-Syndrome: Treatment

- *Pressure relief (comfortable shoes, avoidance of friction, and heat) ( A, LoE 5)*
- *Intensive skin care of hands and feet (Urea hand and foot cream/ ointment, for example Eucerin® 10 %) (B, LoE 1b)*
- *Cooling hand and foot during infusion with Docetaxel (0, LoE 2b)*

## + HFS ≥ grade 3:

- **MUST: Dose reduction/ enlargement of therapy intervals** adapted to substance (A, LoE 5)
- **SHOULD: Topical Steroids (B, LoE 5)**
- **CAN: Hydrocolloid dressing plantar (0, LoE 2b)**

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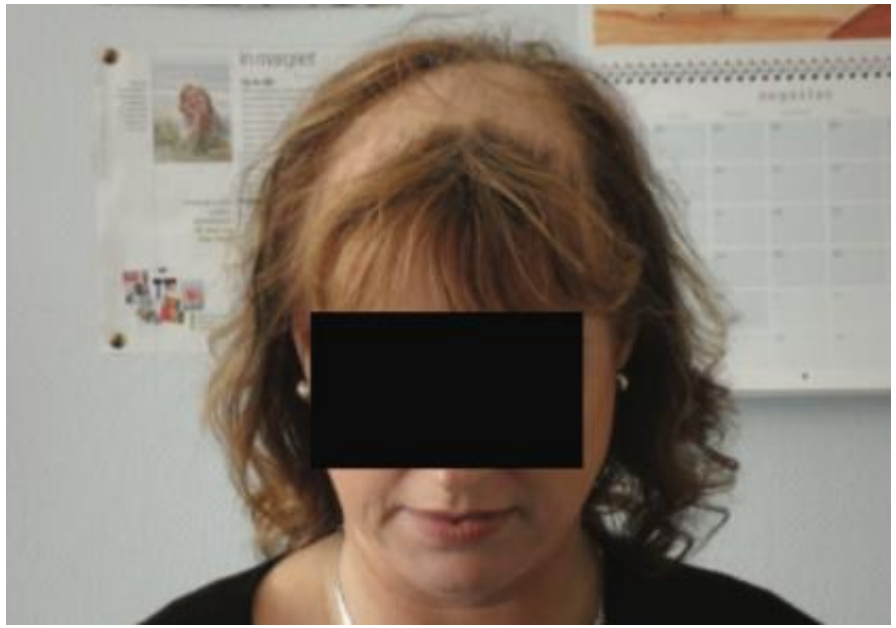
# ALOPECIA



For consideration: study endpoint

# Frequency of alopecia in classical chemotherapy

| Frequently | Occasionally | Rare |
|---|---|---|
| Cyclophosphamide | Amsacrin | Carboplatin, Cisplatin |
| Daunorubicin, Doxorubicin, Epirubicin | Bleomycin | Capecitabine |
| Docetaxel, Paclitaxel | Busulfan, 5-FU | Carmustin |
| Etopsid, Ifosfamid | Cytarabine, Gemcitabine | Fludarabine |
| Topotecan, Irinotecan | Lomustin, Melphalan | 6- Mercaptopurin |
| Vindesin, Vinorelbin | Thiotepa | Methotrexat, Mitoxantron |
| | Vinblastin, Vincristin | Procarbazin, Streptozotocin, Raltritrexed |

Trueb, 2010
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# Scalp cooling?

# Prophylaxis of alopecia

| 8.11. | Evidence-based recommendation |
|---|---|
| **Recommendation grade** **0** | In order to prevent high-grade chemotherapy induced alopecia, scalp-cooling **can be** offered in chemotherapy after risk-benefit-evaluation. |
| Level of Evidence **2b** | Literatur : (Edelstyn, MacDonald et al. 1977, Lovejoy 1979, Kennedy, Packard et al. 1983, Satterwhite and Zimm 1984, Villani, Inghirami et al. 1986, Parker 1987, Robinson, Jones et al. 1987, Giaccone, Di Giulio et al. 1988, Peck, Mitchell et al. 2000, Macduff, Mackenzie et al. 2003, Mols, van den Hurk et al. 2009, Kargar, Sarvestani et al. 2011, van den Hurk, Breed et al. 2012, Betticher, Delmore et al. 2013, Shin, Jo et al. 2015) |
| Vote in the Plenum | Strong consensus |

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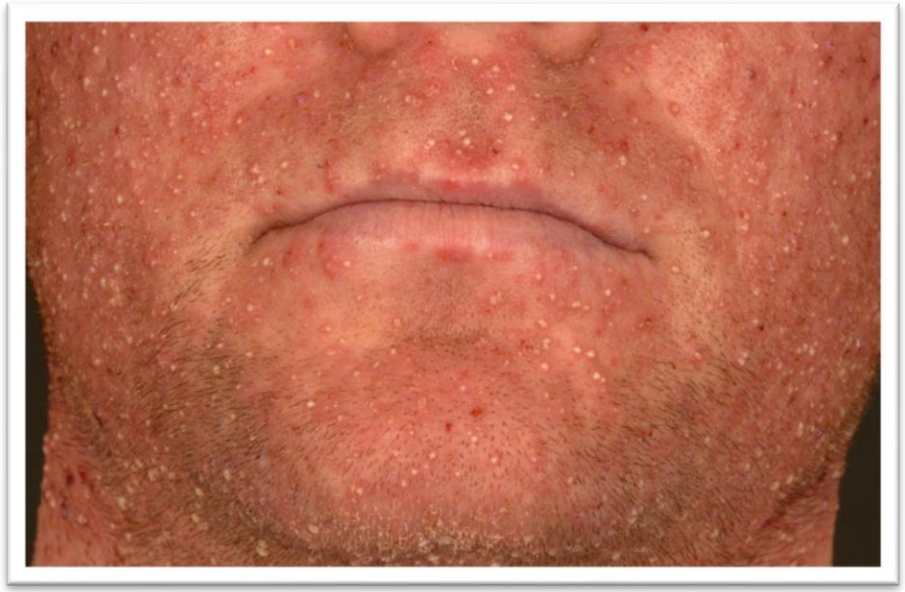
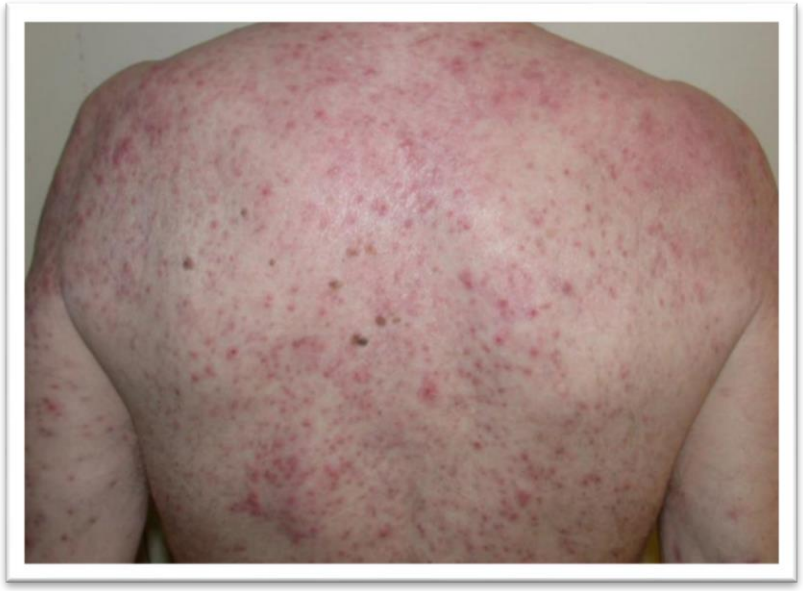
# Acneiform Exanthema (Rash)



www.enzyklopaedie-dermatologie.de
Professor Dr. med. P. Altmeyer



www.oncologypro.esmo.org
Prof. Dr. Siegfried Segaert

# Incidence Skin Toxicity EGFR Inhibition

**small molecules:**

- Erlotinib
- Gefitinib
- Lapatinib
- Vandetanib

→ 5-9 %

**Antibodies:**

- Cetuximab
- Panitumumab

→ 10-17 %

Lacouture et al.: Support Care Cancer (2011) 19:1079–1095

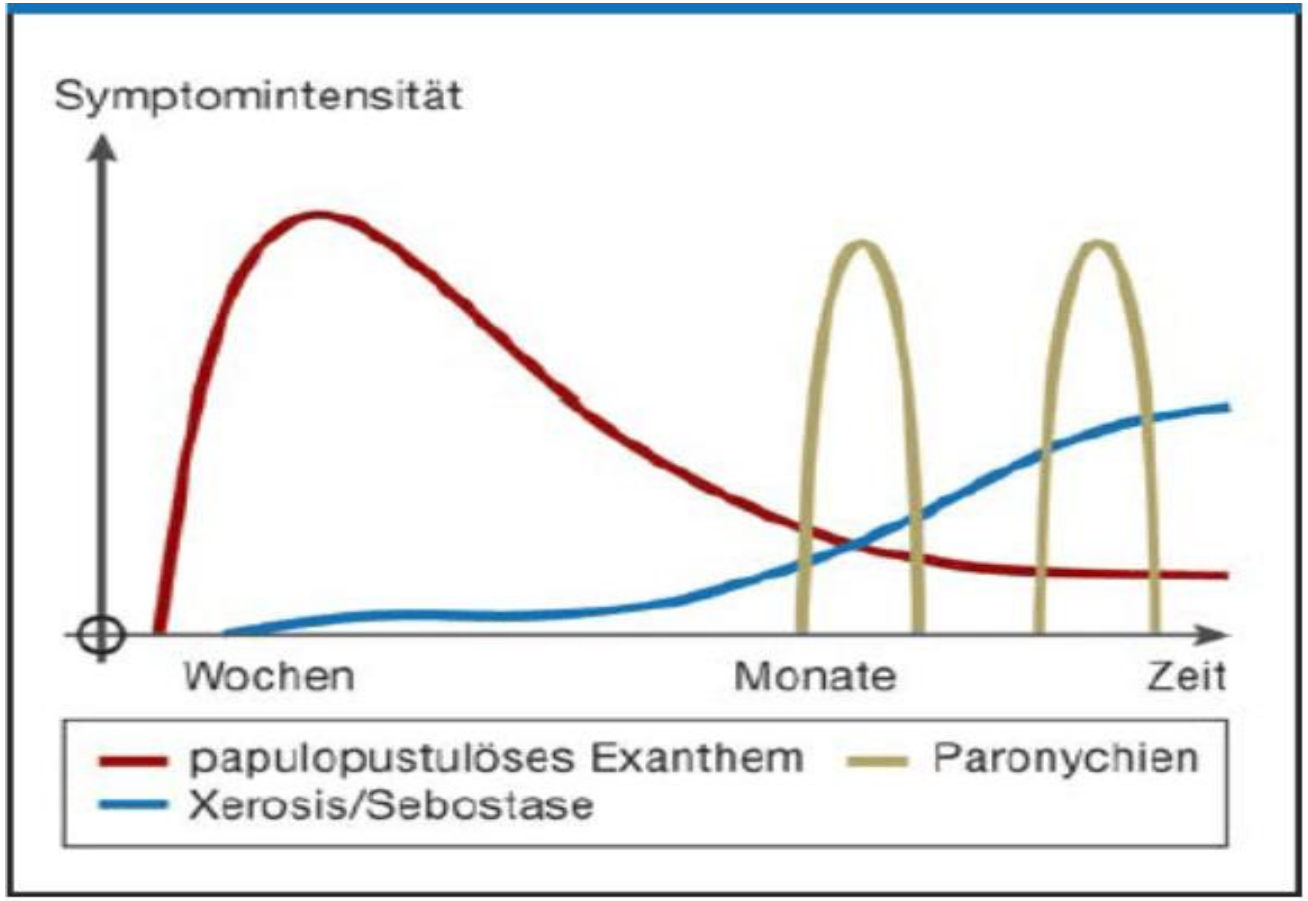
# Acneiform rash

## Comparison NCI CTC Version 3.0 and Version 4.0

| NCI CTC version | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **3.0** | Macular or papular eruption of erythema without associated symptoms | Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering < 50% of BSA | Severe, generalized erythroderma or macu-lar, papular or vesicular eruption; desquamation covering ≥ 50% BSA | Generalized exfoliative, ulcerative, or bullous dermatitis |
| **4.0** | 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 | Papules and / or pustules covering > 30% 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 % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with exten-sive superinfection with IV antibiotics indicated; life threatening conse-quences |

# Time course skin toxicity

## Gutzmer R, Dtsch Arztebl Int 2012; 109(8): 133–40.




Intensity and time course of the most common cutaneous side effects with EGFR inhibition.

# Rash-Propylaxis

**MUST:** Basic therapy under EGFR inhibition (A, LoE 5)
*(avoiding mechanical ,chemical noxes, UV-protection, ph-neutral skin-care, urea-containing cream)*

**SHOULD:** Prophylactic administration of tetracyclines* to reduce the severity of acneiform exanthema (B- LoE 1b)

* Minocylince 2x50 mg/day or Doxycycline 2 x 100 mg / day
The most often used schema in studies were 8 weeks

**CAN/ CANNOT:** No recommendation for or against the use of topical steroids (0, LoE <2)

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# Vitamin K cream in prophylaxis?

**8.1.4.1.2. Vitamin K**

| | |
|---|---|
| 8.4. | Evidence-based statement |
| Level of Evidence <2* | Due to lack of evidence from randomized controlled trials, no recommendation can be made for or against topical prophylaxis of the EGFR-induced acneiform exanthema with vitamin K. |
| Vote in the Plenum | Strong consensus |

*De novo search was carried out to the level of RCTs

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# Rash-Therapy I

*depending on the severity of the acneiform exanthema:*

**CTCAE grade 1**:

SHOULD Basic therapy including oral antibiotics

Topical treatment with antibiotic-containing cream 2x/d (e.g. metronidazole, nadifloxacin)

**(B, LoE 5)**

**CTCAE grade 2**:

SHOULD: Therapy as for CTCAE grade 1
Topical steroids class 2-3 (prednicarbate )

**(B, LoE 5)**

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# Rash-Therapy II

*depending on the severity of the acneiform exanthema:*

**CTCAE grade 3/4**:

SHOULD: Therapy as for CTCAE grade 2

Systemic glucocorticoids

Systemic antibiotic therapy (antibiogramm!)

Possibly isotretinoin (CAVE: never in combination with systemic antibiotics, danger of brain edema!)

**(B, LoE 5)**

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# Vitamin K in therapy

**8.1.4.1.2. Vitamin K**

| | |
|---|---|
| 8.4. | Evidence-based statement |
| Level of Evidence <2* | Due to lack of evidence from randomized controlled trials*, no recommendation can be made for or against topical therapy of the EGFR-induced acneiform exanthema with vitamin K. |
| Vote in the Plenum | Strong consensus |

*De novo search was carried out to the level of RCTs

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# PRURITUS

# Pruritus

| Drug | Incidence Pruritus | Incidence Pruritus ≥ grade 3 |
|---|---|---|
| Axitinib | 8,3 % | 3,9 % |
| Cetuximab | 18,2 % | 2,1 % |
| Erlotinib | 20,8 % | 2,3 % |
| Gefitinib | 21,0 % | 1,0 % |
| Ipilimumab | 30,7 % | 1,0 % |
| Lapatinib | 14,6 % | 1,0 % |
| Panitumumab | 54,9 % | 2,6 % |
| Pazopanib | 2,2 % | 1,1 % |
| Vandetanib | 9,1 % | 0,5 % |

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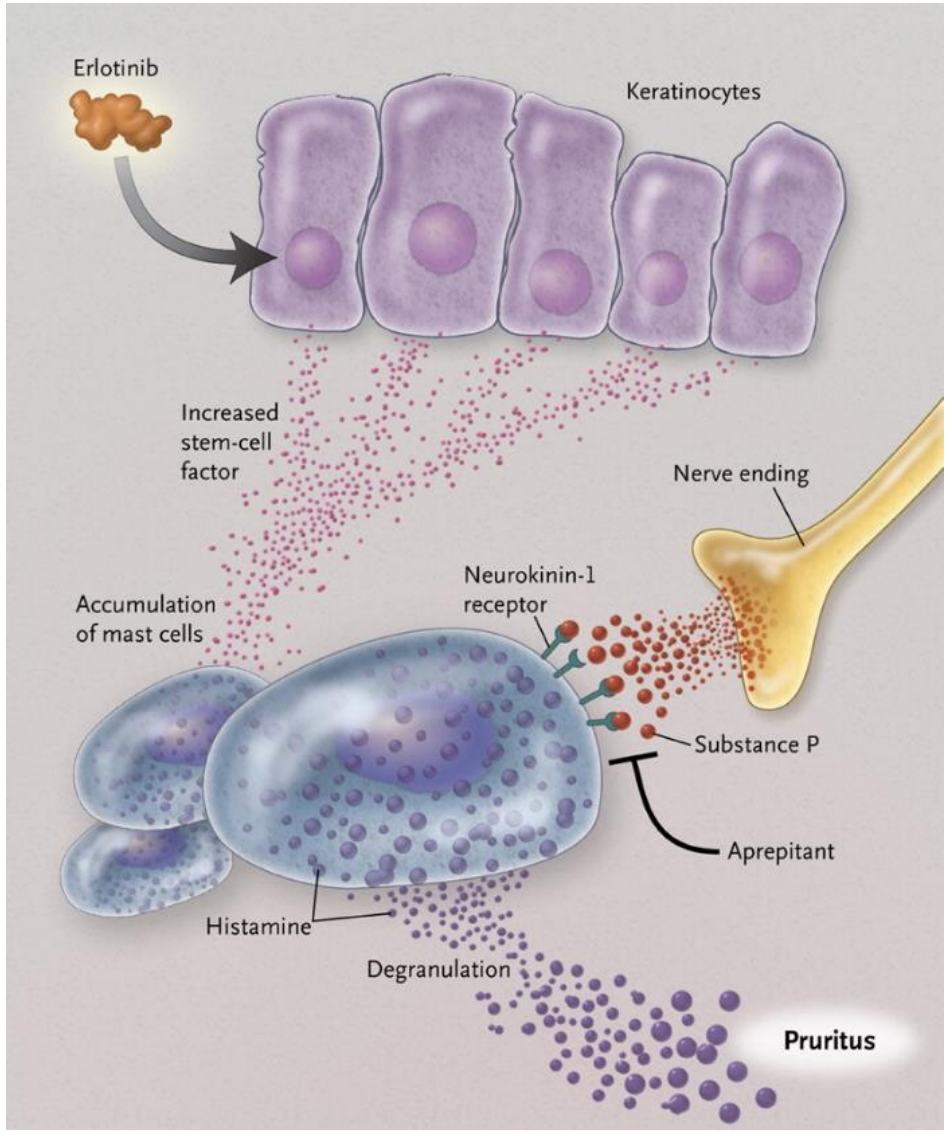
Incidence of Pruritus (Ensslin, Rosen et al. 2013)

# Pruritus-Therapy

| 8.123. | Consensus-based recommendation |
|---|---|
| Recommendation grade A | The basic treatments for the therapy of pruritus in EGFR inhibitor therapy should be continued: |
| | The further therapy of pruritus depends on the severity: |
| Recommendation grade B | In patients with pruritus **CTCAE grade 1**, further therapy should be done with:<br>• Re-freasing external and<br>• **Consider oral antihistamines** |
| Recommendation grade B | In patients with pruritus **CTCAE grade 2**, further therapy should be done with:<br>• Re-freasing external and<br>• Oral antihistamines<br>• **Consider topical glucocorticoid, class 2** (prednicarbate cream) |
| Recommendation grade B | In patients with pruritus **CTCAE grade 3**, further therapy should be done with:<br>• Re-freasing external and<br>• Oral antihistamines<br>• Topical glucocorticoid, class 2 (prednicarbate cream) |
| Level of Evidence | Literatur: S3 Guideline Supportive Care in Cancer Patients: Karin Jordan Guideline coordinator, Franziska Jahn Guideline secretary 2016, AWMF Register-No: 032-054OL |

# ANY OTHER EVIDENCE?

# Erlotinib-induced pruritus




- Subtance P leads to degranulation of mast cells – distribution of pruritogens
- NK-1- receptor blockade can prevent granulation
- Aprepitant is an NK-1-RA

Gerber et al., N Engl J Med. 2011 Feb 3;364(5):486-7

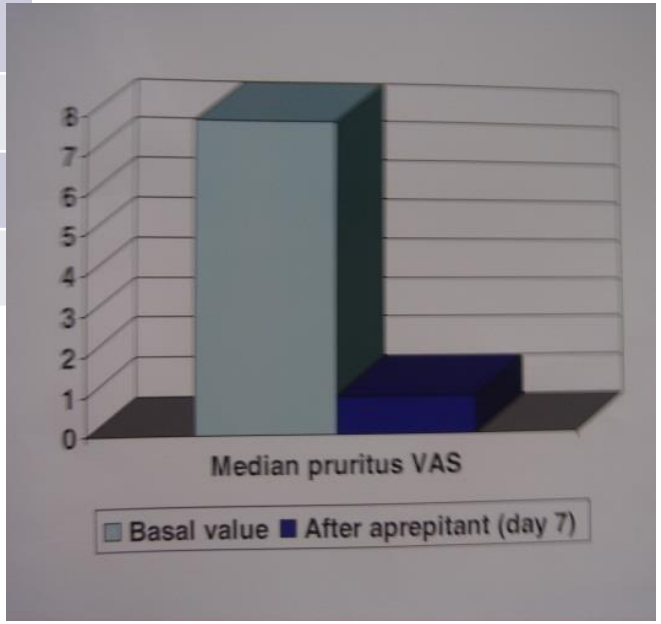
# Aprepitant is active in biologic therapies induced severe pruritus: Proof of concept study.

*D. Santini, 2012*

- Prospective study (22 patients)
- 91 % of patients responded to Aprepitant (decrease > 50 %), 2 did not.

| Pruritus | Baseline | | Pruritus | After 1 week |
|---|---|---|---|---|
| VAS 9 | 6 | | VAS 6 | 1 |
| 8 | 12 | | 4 | 1 |
| 7 | 4 | | 1-3 | 10 |
| | | | 0 | 10 |

„Pruritus-Median“: 8 „Pruritus-Median“: 1



# Pruritus-Therapy-

## Step scheme similar to Rash:

**Basis treatment**

**+**

**Oral antihistamines**

**+**

**Topical steroid**

**...and can be helpful**

### 8.5.6.1. Aprepitant

| | |
|---|---|
| 8.124. | Evidence-based recommendation |
| Recommendation grade 0 | In the case of treatment-resistant pruritus under EGFR inhibitor therapy, administration of **aprepitant** can be carried out in addition to the treatment initiated **(off label use)** |
| 2b | Literatur:<br>(Santini, Vincenzi et al. 2012) |
| Vote in the Plenum | Strong consensus |

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# What else is important?

- Patient needs to be informed about these toxicities
  - Close collaboration with dermatologists

    (highly potent steroids, isotretinoin)