“ Management of symptoms and adverse events”

Phichai Chansriwong, MD

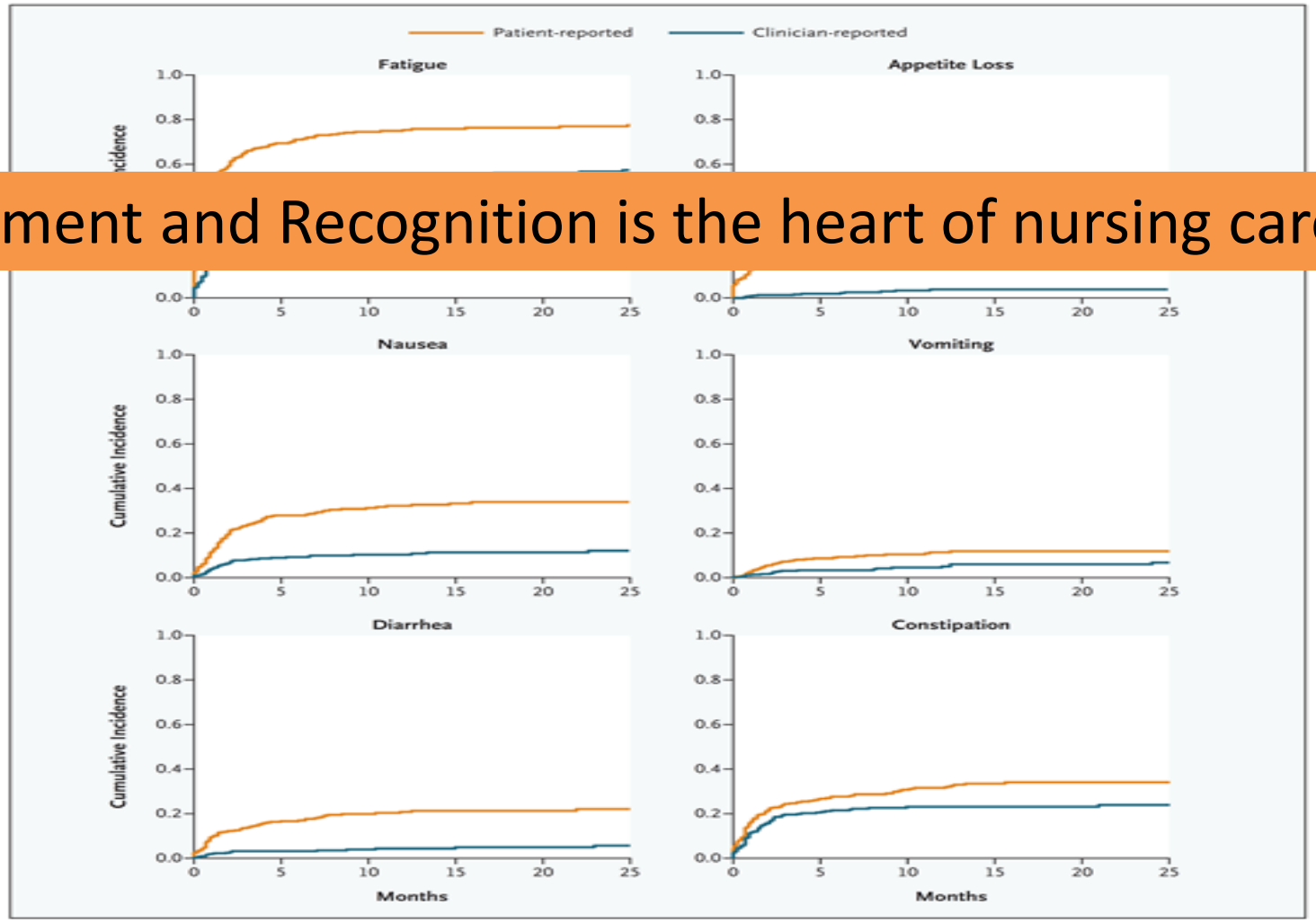
Quality of Life in patient's perspectives: 5 items

- Adequate pain and symptom management
- Avoid inappropriate prolongation of dying
- Achieving a sense of control
- Relieving burden
- Strengthening relationships with loved ones

  - Quality End-of-Life Care: Patient's Perspectives, JAMA 1999 281(2) 163-168

The Missing Voice of Patients

Assessment and Recognition is the heart of nursing care



Cumulative Incidence of Adverse Symptom Events over Time as Reported by Patients versus Clinicians at Successive Office Visits.

n engl j med 362;10 march 11, 2010

MADRID 2014 ESMO congress

Association between patient reporting (any severity) and physician reporting (any grade) – 2482 cycles

	Anorexia	Nausea	Vomiting	Constipation	Diarrhea	Hair loss
Toxicity reported by:						
Patient: NO Physician: NO	51.4%	44.5%	76.7%	59.3%	73.1%	55.6%
Patient: NO Physician: YES	2.4%	10.1%	6.4%	3.2%	4.2%	1.7%
Patient: YES Physician: NO	37.0%	24.6%	9.7%	29.7%	13.9%	28.8%
Patient: YES Physician: YES	9.2%	20.8%	7.2%	7.8%	8.9%	13.9%
Under-reporting by physicians	**80.2%**	**54.2%**	**57.5%**	**79.2%**	**61.0%**	**67.4%**

Benefit vs Risk Ratio of Adjuvant Chemotherapy

Side effects of chemotherapy

- 1. Immediate

- Anaphylactic shock
- Cardiac arrhythmia
- Pain at the site of injection

Side effects of chemotherapy

2. Early

- Nausea, vomiting
- Fever
- Hypersensitivity reactions
- Flu-like syndrome
- Cystitis

Side effects of chemotherapy

3. Intermediate (within days)

a) Bone-marrow depression

- after 1-3 weeks (majority of drugs)
- after 4-6 weeks (nitrosoureas)

b) Stomatitis

c) Diarrhea

d) Alopecia

e) Peripheral neuropathy, loss of reflexes

f) Paralytic ileus

g) Renal toxicity

h) Immunosuppression

Side effects of chemotherapy

4. Late (within months)

- - Injury to vital organs or system
  - heart adriamycin;
  - Lung bleomycin and busulfan
  - Liver methotrexate
- Effects on reproductive capacity

  (amenorrhea, decreased sperm Conc.)
- Carcinogenic effects

Alkylating agent
Cyclophosphamide: Hemorrhagic cystitis

- A unique toxicity of cyclophosphamide and other oxazaphosphorines
- Due to irritation of the bladder mucosa by urinary metabolites (esp. *acrolein*, but phosphoramide mustard and chloroacetaldehyde may contribute to this toxicity).
- *Mesna* and careful attention to hydration of patients and emptying of the bladder are crucial for high-dose administration.

Alkylating agent–associated secondary leukemia

- More than ten years of onset.
- Frequently preceded by a preliminary myelodysplastic syndrome.
- Commonly have deletions of chromosome 5 or 7.

Cisplatin: Toxicities

- **Nephrotoxicity:**
  - Dose related and cumulative
  - Manifested primarily by decrease in CCr.
  - Defects in tubular (especially proximal) resorption.
    - Hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia
  - Higher doses require aggressive hydration.

Cisplatin: Toxicities

Prevention for nephrotoxicity,

- Prehydrate with at least 500 mL of NSS
- Diuresis: before administration, mannitol (12.5-25.0 g) IV , even though there is no evidence of renoprotection. ?
- Magnesium supplementation
- Amifostine - demonstrated statistically significant protection, while preserving the antitumor efficacy of cisplatin.
- Not combined with renal tubular toxins

Cisplatin: Toxicities

- **Ototoxicity:**
  - Recognition
  - cumulative and irreversible side effect
  - results from damage to the inner ear.
  - Audiograms are recommended every two to three cycles.
  - The initial audiographic manifestation is loss of high-frequency acuity (4000 to 8000 Hz).

Vincristine: Toxicities

- **Neurotoxicity:**
  - peripheral, symmetric mixed sensory-motor, and autonomic polyneuropathy.
  - Severe neurotoxicity is observed infrequently with VBL and VDS.
  - Initial manifestations of neurotoxicity are depression of the DTRs and paresthesias of the distal extremities.
  - Vibration sense, position sense, pinprick sensation, and two-point discrimination are generally unaffected.

Vinca Alkaloids :Vesicant

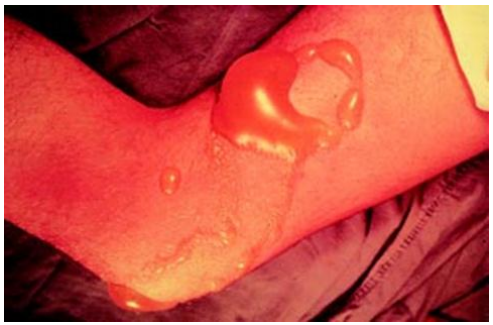
- **Vesicants:** Vinca alkaloids may cause tissue damage if extravasation occurs and *should not be administered IM, SQ, intravesically, or intraperitoneally.*

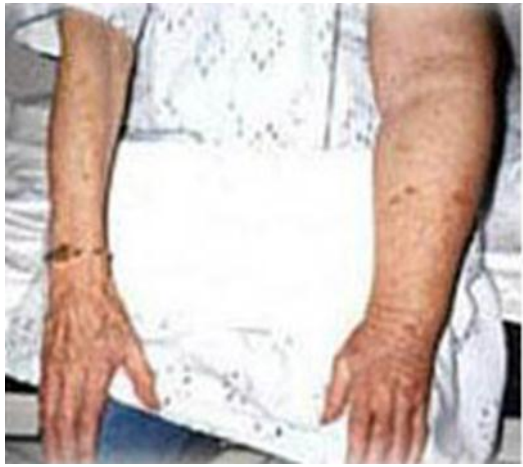
  Treatment

  - Discontinued, and
  - Aspiration of any residual drug remaining in the tissues should be attempted.

Vinca Alkaloids :Vesicant

- The immediate application of *heat* for 1 hour four times daily for 3 to 5 days.
- The injection of *hyaluronidase*, 150 to 1500 U (15 U/mL in 6 mL 0.9% sodium chloride solution) SQ, q 6hr in a circumferential tissue
- A surgical consultation to consider early débridement is also recommended.





TAXANES : Side effect

- **Major hypersensitivity reactions:**
  - 1% to 3% after development of effective prophylaxis.
  - Characterized by dyspnea, bronchospasm, urticaria, hypotension, chest, and abdominal and back pain
  - Usually occur within the first 10 minutes after the first (and less frequently after the second) treatment and resolve completely after stopping treatment.
  - Recommended premedication:
    - dexamethasone, 20 mg po or IV, 12 and 6 hr before treatment;
    - an H1-receptor antagonist (e.g., diphenhydramine, 50 mg intravenously) 30 min before treatment;
    - an H2-receptor antagonist (e.g., cimetidine, 300 mg; or ranitidine, 150 mg intravenously) 30 min before treatment

Docetaxel: side effect

- **Fluid retention syndrome**
  - Premed: steroids
  - Characterized by edema, weight gain, and third-space fluid collection.
  - Cumulative and not appear to be due to hypoalbuminemia or cardiac, renal, or hepatic dysfunction.

5-Fluoropyrimidines: Toxicities

- **Gastrointestinal toxicity:**
  - **Mucositis**.
  - Diarrhea

    -watery or bloody, and the combination of nausea, vomiting, and profuse diarrhea can lead, in some cases, to profound dehydration.

    - Antidiarrheal agents such as diphenoxylate and loperamide :mild to moderate diarrhea.

    - Not response to medications, the somatostatin analogue octreotide has been effective.

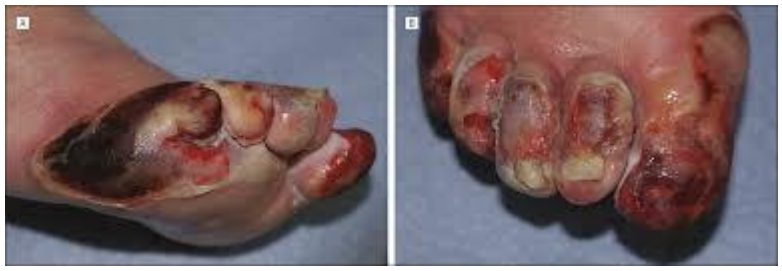
Dermatologic toxicities 5-Fluoropyrimidines

- Photosensitivity reactions:

  - increased pigmentation over the veins into which 5-FU administered.

  - more generalized hyperpigmentation, and atrophy also occur.

- Hand-foot syndrome, Palmar-Plantar Erythrodysesthesia



5-Fluoropyrimidines: side effect

- **Cardiotoxicity:**
  - chest pain, cardiac enzyme elevations, and ECG changes consistent with myocardial ischemia.
  - vasospasm as a possible mechanism.

Irinotecan: Toxicities

- **Cholinergic syndrome**
- Irinotecan is a weak inhibitor of acetylcholinesterases
  - Early-onset diarrhea, flushing, bradycardia, tearing, diaphoresis, and visual accommodation symptoms, abdominal cramping, fatigue, alopecia, nausea, and vomiting.
  - Treated : atropine premedication to those patients who experience this adverse reaction

Irinotecan: Toxicities

- **Diarrhea:** Dose limiting toxicity

  1. Acute diarrhea: seen immediately after drug administration

  2. Delayed-onset diarrhea: occurring at least 24 hours after drug administration

  - potentially life threatening

  - Patients should be instructed to take high-dose loperamide at the first onset of diarrhea, and administered continuously until all diarrhea has stopped for at least 12 hours.

Anthracyclines : side effect

- **Cardiac toxicity:**
  - characterized by acute and chronic effects.
  - Cumulative exposures
    - Total doses of bolus doxorubicin greater than 400 to 550 mg/m² should not be exceeded during a patient's lifetime,
    - *Serious cardiac dysfunction can occur with any anthracycline.*
    - *Chronic effects: Most often starting after 1 year of treatment.*
      - *Typically irreversible*

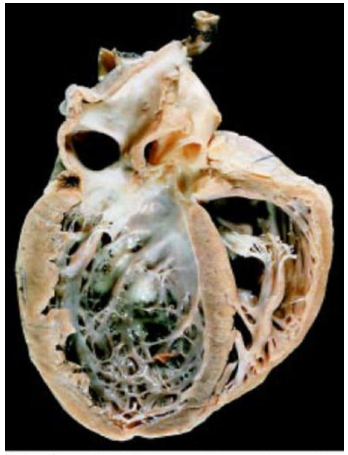


Fig. 4 – Dilated cardiomyopathy secondary to treatment with anthracyclines: dilation with thinning of the ventricular walls (longitudinal section).

Anthracycline cardiotoxicity

Doxorubicin-induced cardiotoxicity is related with cumulative dose

Conventional doxorubicin-related CHF was

- 5% at a cumulative dose of 400 mg/m2,
- 16% at a dose of 500 mg/m2
- 26% at a dose of 550 mg/m2

Age was risk factor,

- hazard ratio (HR) of 2.25 in patients older than 65 years compared with those aged 65 years or younger.

Anthracyclines : side effect

- **Potent vesicant**
  - Severe tissue necrosis requiring surgical débridement and skin grafts can ensue after drug extravasation.
  - Acute treatment with ice and dimethyl sulfoxide (DMSO) may minimize extravasation-induced tissue damage.

Bleomycin: Toxicities

- **Pulmonary toxicity:**
  - Dose-limiting toxicity
  - ~ 10% of patients
  - The risk is increased in
    - patients older than 70 years of age
    - total cumulative dose > 400 units.
    - underlying lung disease;
    - prior irradiation to the chest or mediastinum
    - exposure to high concentrations of FIO2.

Requirement before starting chemotherapy administration

Disease factors

Pathological report of malignancy

Evidence of chemotherapy regimen efficacy

Goal of treatment

Review history of previous treatment

- Monitoring of tumor response
- Management of chemotherapy induced toxicities

Chemotherapy with limited cumulative toxicity

Drug	Long term toxicity	Cumulative dose	Comments
Doxorubicin Epirubicin	Dilated cardiomyopathy (DCM)	450 mg/m^2 900 mg/m^2	อุบัติการณ์ <5% ถ้าใช้ไม่เกิน ↑ incidence in previous cardiovascular disease, bolus, ↑age, RT to chest
Bleomycin	Pulmonary fibrosis		
Oxaliplatin	Neuropathy	Stop temporally if patient evidenced neuropathy > gr 2. Drug can be re-start if toxicity ↓ to </= gr 1	

Management of chemotherapy induced toxicities

Expected common toxicities from chemotherapy treatment

Adverse events	Short name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophi (ANC)						eath
Platelets						eath
Asthenia						
Diarrhea						eath
Vomitting						eath
Mucositis						
Neurosens						eath
		not interfering ADL	interfering with function but not ADL	interfering with ADL		

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Management of chemotherapy induced toxicities

MASCC/ESMO ANTIEMETIC GUIDELINE 2016

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WWW.MASCC.ORG

ESMO
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European Society for Medical Oncology

Multinational Association of Supportive Care in Cancer

Organizing and Overall Meeting Chairs:
Matti Aapro, MD
Richard J. Gralla, MD
Jørn Herrstedt, MD, DMSci
Alex Molassiotis, RN, PhD
Fausto Roila, MD

Requirement before starting chemotherapy administration

Disease factors

Review history of previous treatment

- - Team

--Host factors
AGE?

Performance status
Underlying disease
Safety factors

Cancer chemotherapy administration: **Team**

1. Specific knowledge and experience of the side effects and toxicities of the various cytostatic drugs
2. Broad medical knowledge
3. Knowledge of the natural course of all neoplastic diseases
4. Staging and therapeutic strategy

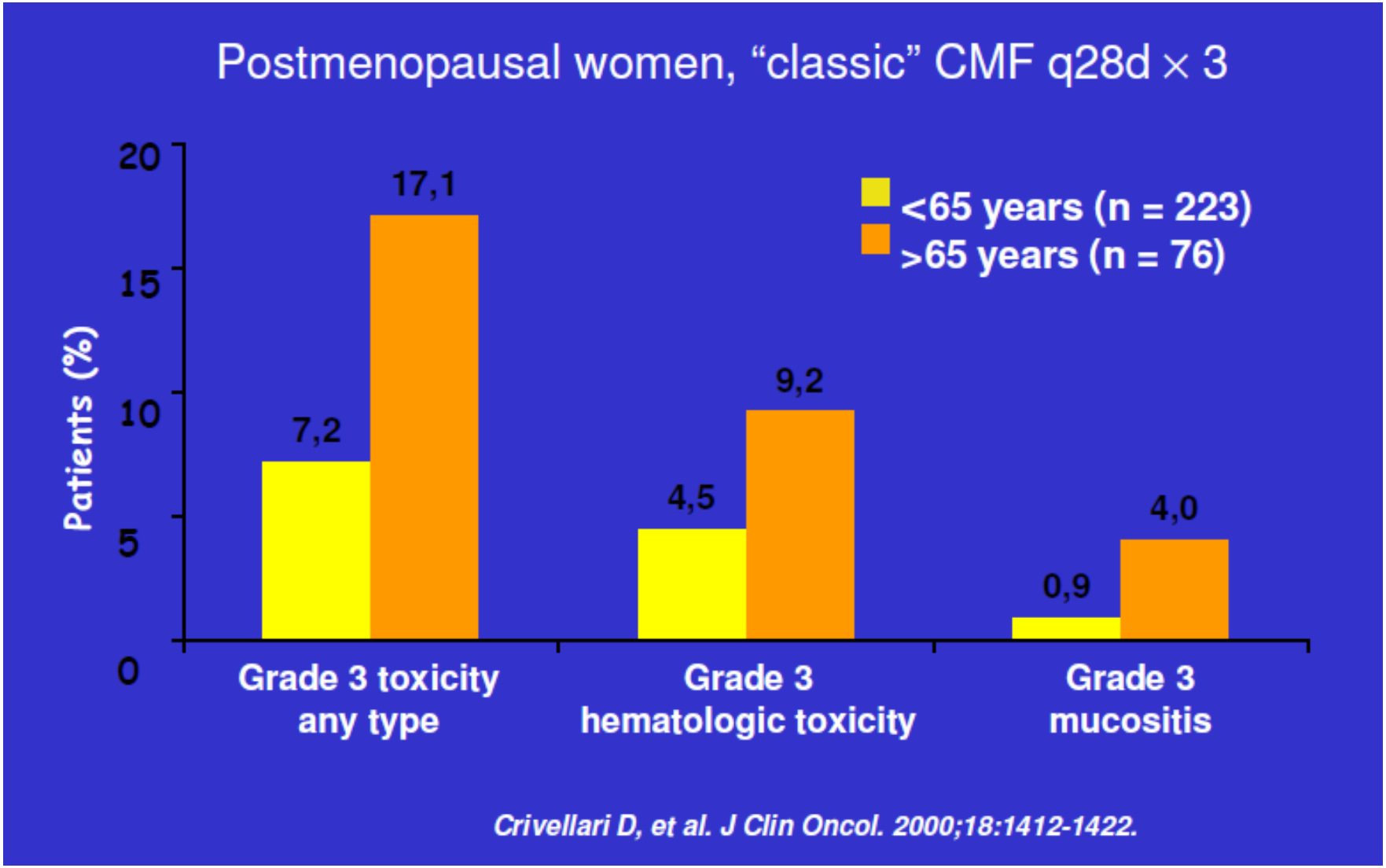
Who is elderly?

What else do we need to know?

Chemobrain: elderly

- CNS (encephalopathy of various severities):
  - methotrexate, vincristine, ifosfamide, fludarabine, cytarabine, 5-fluorouracil, cisplatin ,cyclosporine and the interferon
  - PNS: Falling risk

Bone marrow Tolerance to Chemotherapy Lessens With Age



Comorbidity

- The impact of comorbidity on overall survival
- three or more comorbid conditions: frail patient
- breast cancer who had 3 or more of seven selected comorbid conditions had a 20-fold higher rate of mortality

William A et al. annual internal med.

15 jan 1994, Vol 12 issue 12

Performance status

Eeatern Coorperative Oncology Group (ECOG) Performance Status

PS 0	Asymptomatic, normal activity	ทำกิจวัตรได้ตามปกติ ทำงานหนักได้
PS 1	Fully ambulatory, symptomatic, able to perform activities of daily living	ทำกิจวัตรประจำวันได้ปกติ ทำงานได้แต่หนักมาก มีอาการนิดหน่อย
PS 2	Symptomatic, up and about, in bed < 50% of daytime	มีอาการเหนื่อย ทำกิจ วัตรประจำวันยังได้ แต่ต้องมีการพักระหว่างวันแต่น้อยกว่าร้อยละ 50
PS 3	Symptomatic, capable of only limited self-care, in bed > 50% of daytime	มีอาการเหนื่อยมากขึ้น ทำกิจวัตรประจำวันได้แต่ไม่ทุกอย่าง ต้องพักระหว่างวันมากกว่าร้อยละ 50
PS 4	Completely disabled, cannot perform any self-care, bedridden 100% of time	มีอาการมาก ไม่สามารถทำกิจวัตรได้เอง และต้องนอนพักตลอดเวลา
PS 5	Dead	เสียชีวิต

Basic chemotherapeutic agent calculation

- BSA (body surface area)
- morbid obesity : BSA > 2.0 m2
  - 1. Ideal body weight for male
    - = 51.65 + (1.85 x (height – 60))
  - Ideal body weight for female
    - = 48.67 + (1.65 x (height – 60))
    - 2. BSA limit at 2.2

DRUGS AFFECTED BY CHANGES IN HEPATIC METABOLISM

	% dose reduction for hepatic dysfuction		
	Mild (bili*1.5-3.0;SGOT**60-180)	Moderate (bili*3.1-5.0;SGOT**>180)	Severe (bili*>5.0)
Anthracyclines			
Andriamycin	50%	75%	Omit
daunorubicin	25%	50%	Omit
Taxanes	Omit	Omit	Omit
Vinca Alkaloids			
Epipodophyllotoxins	50%	Omit	Omit
Methotrexate	0%	25%	Omit
Cyclophosphamide	0%	5%	Omit
5-fluorouracil	0%	0%	Omit

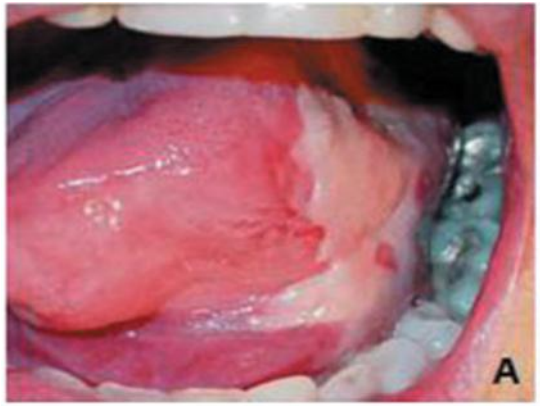
Drugs requiring dose modification in renal dysfunction

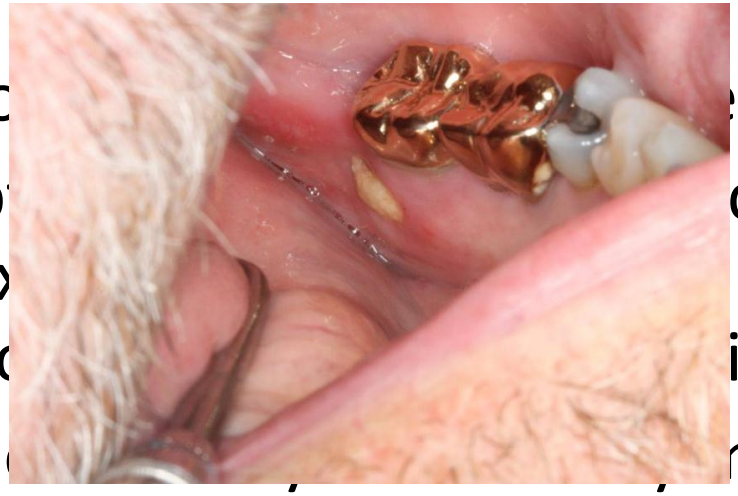
	% dose reduction based on Crcl(ml/min)		
	30-60	10-30	<10
cisplatin	50%	Omit	Omit
carboplatin	20%	30%	30%
cyclophosphamide	0%	0%	50%
bleomycin	25%	25%	50%
methotrexate	50%	Omit	Omit
Nitrosoureas	Omit	Omit	Omit
Capecitabine	75%	Omit	Omit

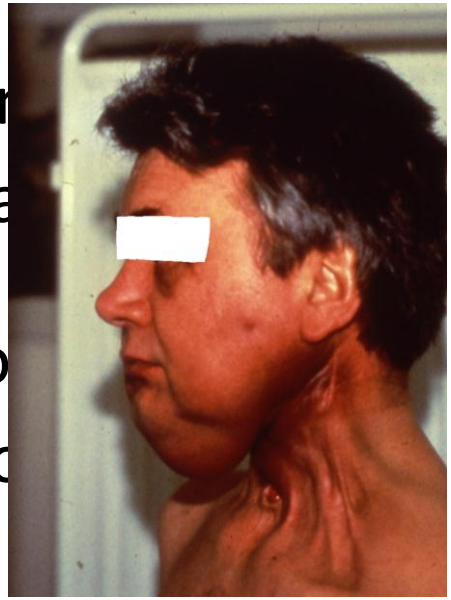
Palliative chemotherapy VS Futility

- Is it therapeutic futility at the end of life?
- “Life is short, the art long”--Medical decision: Hippocrates
- ถามตนเองก่อนเสมอ ว่าเราให้ benefit or risk ให้ผู้ป่วย

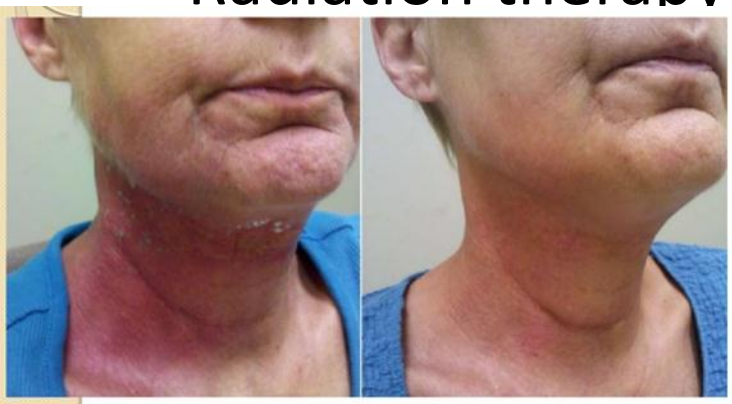
Complication of radiation:

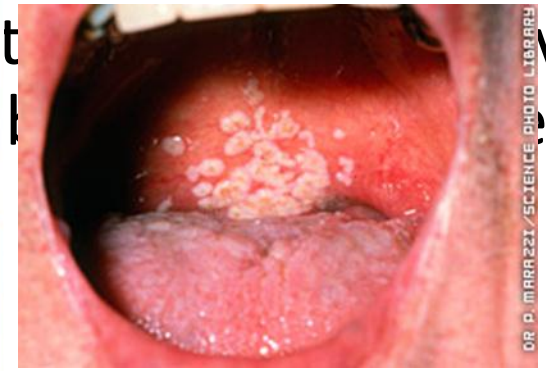


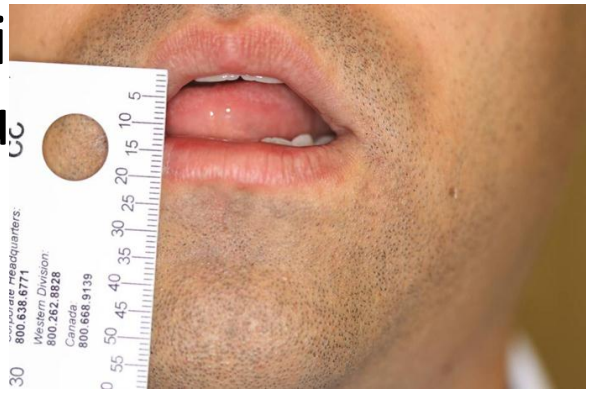




- Long-term squ… …nc… years after radiation therapy.
- Radiation therapy is known to be mutagenic, …vi… …eu…







Hormone: Tamoxifen Toxicity

- **Menopausal symptoms**:
  - 50% - 60% (N.B. 40% - 50% in placebo)
  - MC in premenopausal
  - Vaginal dryness and discharge may occur in excess.
- **Depression**:
  - Maybe seen in as high as 10% of patients.
  - But no randomized comparisons available.
- **Ocular toxicity**:
  - Keratopathy, maculopathy & cataract
  - Reported with high doses
  - However NSABP studies have found no increase in vision threatening ocular toxicity.
- **Thromboembolism**:
  - Severe thromboembolism seen in ~ 1% patients in the preventive setting.
  - Risk up to 10 times that experienced by healthy women
  - Complication more common in elderly patients with metastatic breast cancer and who are receiving CCT
- **Carcinogenesis**:
  - Increased risk of endometrial cancers (hazard rate of 1.7 per 1000 – NSABP B 14 data)
  - Mostly low grade & stage I tumors.
- **Other tumors**:
  - Hepatomas
  - Clear cell sarcomas of ovary

Toxicity of Adjuvant Endocrine Therapy in Postmenopausal Breast Cancer Patients: A Systematic Review and Meta-analysis

Eitan Amir, Bostjan Seruga, Saroj Niraula, Lindsay Carlsson, Alberto Ocaña

7 trials; 30.023 patients

Table 2. Absolute differences and number needed to harm associated with one adverse event of each type

	↑ Cardiovascular disease		= Cerebrovascular disease		↓ Venous thrombosis		↑ Bone fractures		↓ Endometrial Carcinoma	
Trial (reference)	Absolute difference, %	NNH	Absolute difference, %	NNH	Absolute difference, %	NNH	Absolute difference, %	NNH	Absolute difference, %	NNH
ATAC (5)	0.8	129	−0.8	−115	−1.8	−59	4.6	22	−0.6	−163
BIG01-98 (3)	0.9	107	0	∞	−1.8	−56	2.8	36	−0.5	−204
IES (13)	1.3	79	0	∞	−1.2	−84	2.1	48	−0.2	−479
ABCSG8/ARNO (4)	<0.1†	1643†	NS	NS	−0.6	−179	1.1	91	−0.3	−268
ITA (2)	1.3	72	NS	NS	−2.3	−40	NS	NS	−2.2	−46
N-SAS BC03 (14)	−0.3	−354	NS	NS	0.3	347	−1.2	−85	−0.3	−349
TEAM (15)	0.7	139	0.4	311	−1.1	−91	1.6	63	−0.2	−485
Pooled	0.8	132	−0.1	−974	−1.3	−79	2.2	46	−0.4	−258

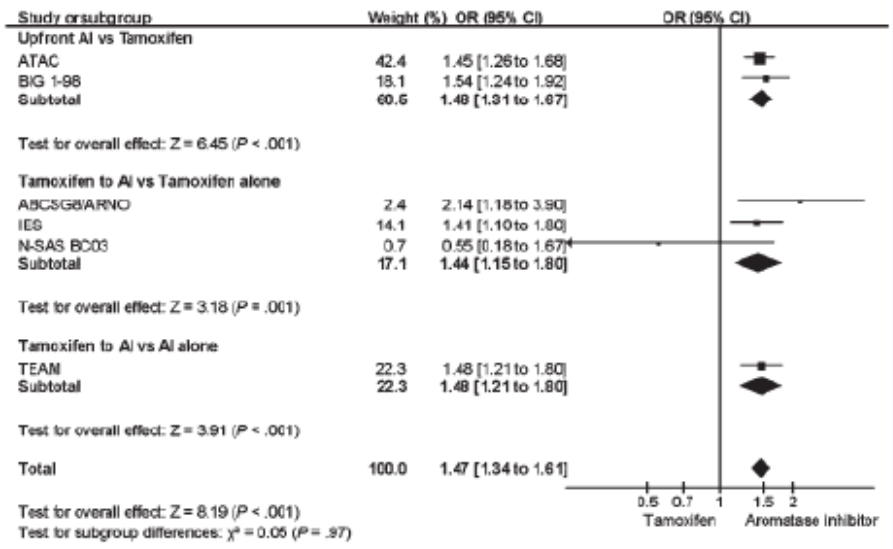
Limitations:

- Literature rather than individual patient data meta-analysis
- Reports of trials with different durations of follow-up
- Information on the potentially confounding baseline host factors (eg, obesity, hypertension, diabetes, and family history of events of interest) or the use of concurrent medications was not reported

J Natl Cancer Inst 2011;103:1299–1309

AI: Bone health

- Adjuvant AI vs TAM: statistically significant increase in bone loss and fractures with AI, regardless of which AI or strategy (upfront or sequential) was used



Difference in absolute risk =2.2%

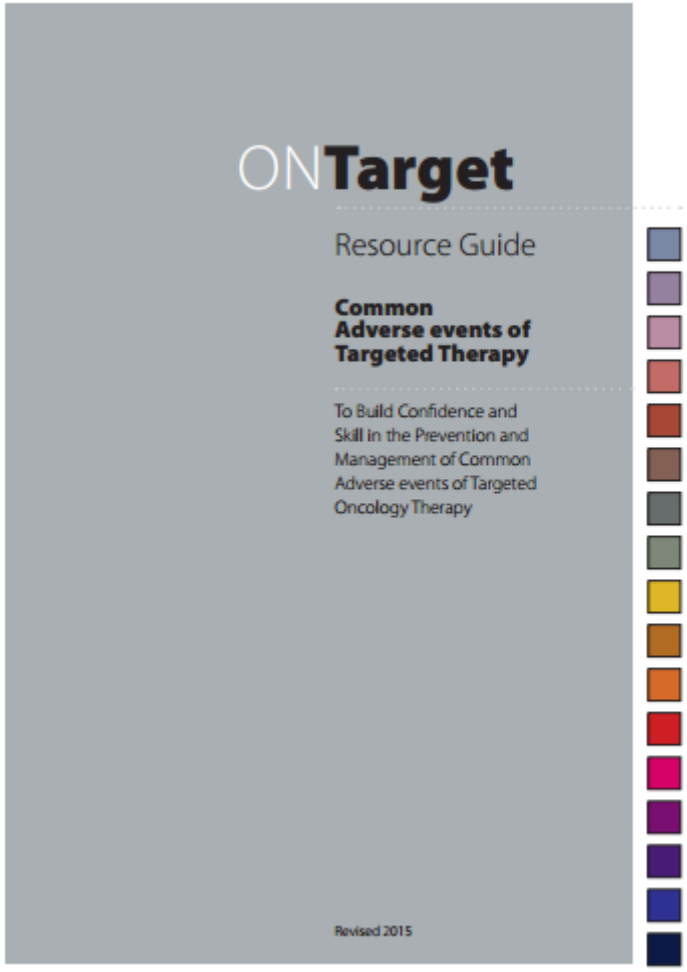
Amir et al. J Natl Cancer Inst 2011;103:1299–1309

AI and Tamoxifen VS Cognition

- After 1 year of adjuvant therapy, tamoxifen use is associated with statistically significant lower functioning in verbal memory and executive functioning (vs healthy controls),
- whereas exemestane use is not associated with statistically significant lower cognitive functioning in postmenopausal patients with BC.

Schilder CM et al J Clin Oncol 2011

Targeted therapy



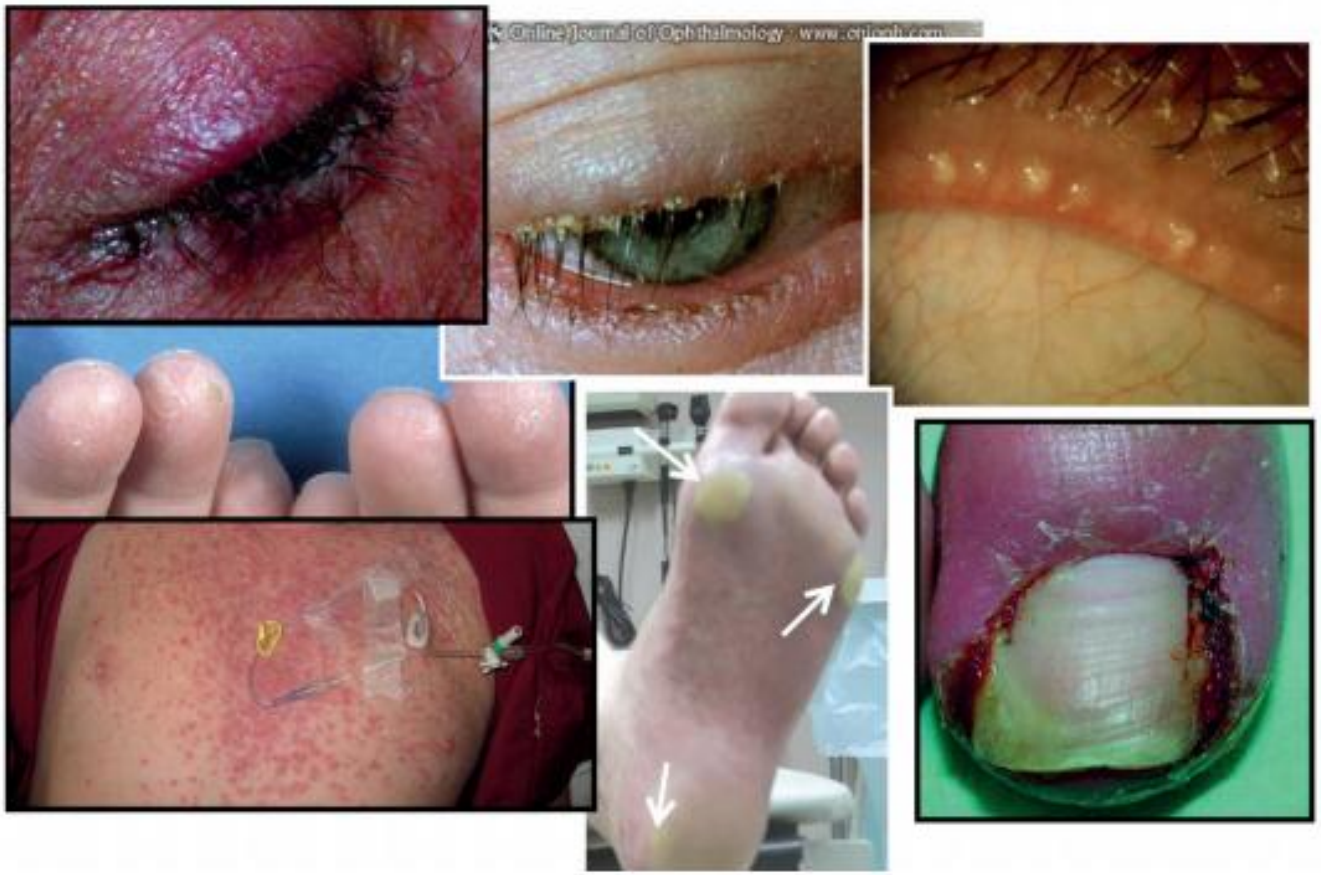
- http://www.capho.org/sites/default/files/page-files/2015%20OnTarget.pdf

Most common mucocutaneous adverse events with targeted agents

- Papulopustular eruption ('rash') 45–100%
- Xerosis cutis (dry skin) 7–35%
- Pruritus (itchy skin) 8–35%
- Hand-foot skin reaction 5–59%
- Periungual inflammation (nail) 12–16%
- Abnormalities in hair growth 14–21%
- Eye/eyelash abnormalities >30%
- Mucosal changes 12–69%

Source: Y Balagula et al. (2011) *Int J Dermatol* 50:129–146

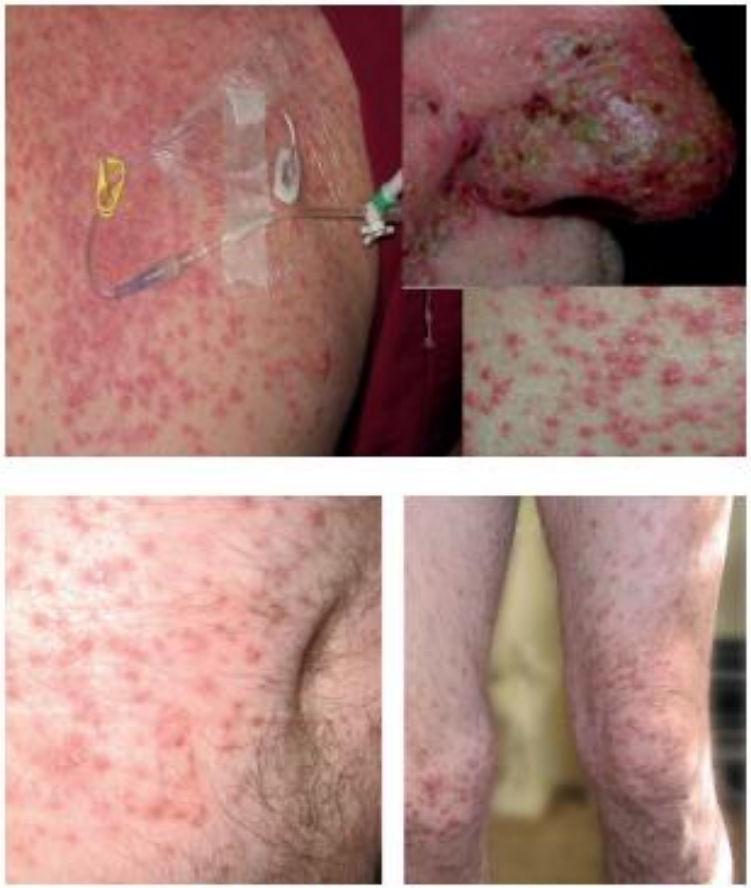
MUCOCUTANEOUS TOXICITIES



Clockwise starting from top left: trichomegaly; blepharitis; meibomitis; paronychia; hand-foot skin reaction; papulopustular eruption; fissures on the hands.

Courtesy of Leiden University Medical Center, Leiden

PAPULOPUSTULAR RASH



This rash starts on the face but then moves to the stomach, legs and arms. It is important to ask patients, because they may have rash where you cannot see it, and they may not tell you.

Courtesy of Leiden University Medical Center (upper images), CB Boers-Doets (lower images)

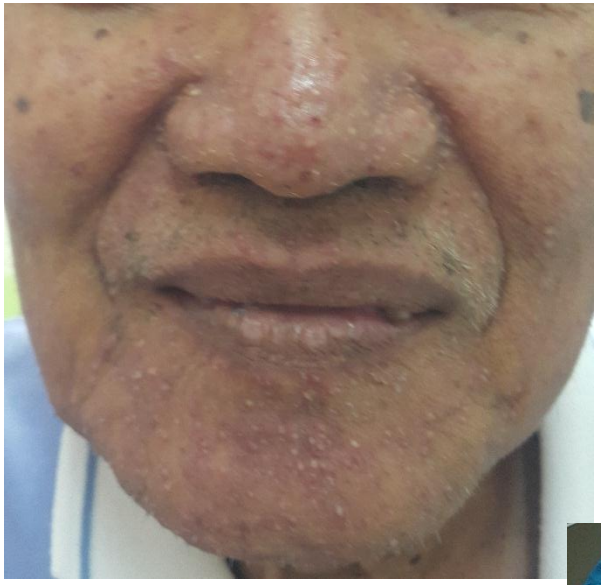
BRAF-SPECIFIC SKIN REACTIONS

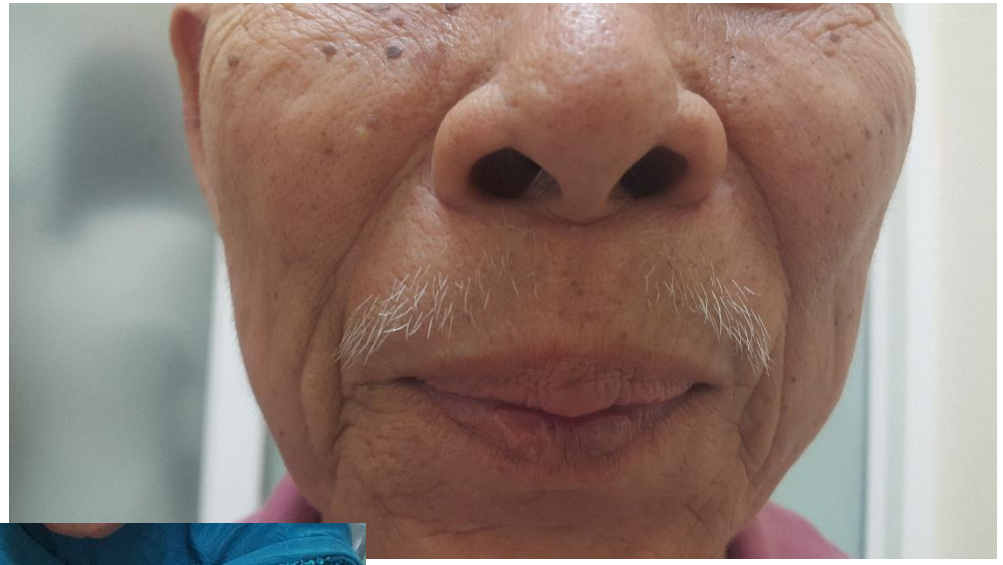
BRAF inhibitors cause a rash over the whole body (left), as well as stem warts (centre), which can be burnt with nitrogen, and squamous cell carcinoma (right), which must be excised.

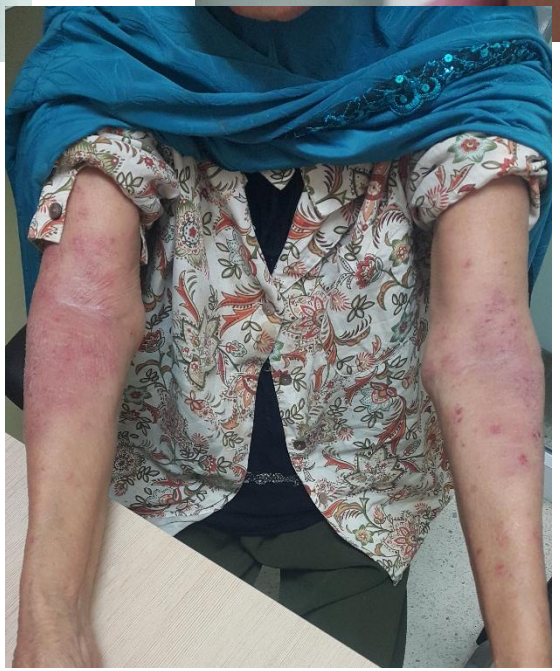
Courtesy of the Netherlands Cancer Institute

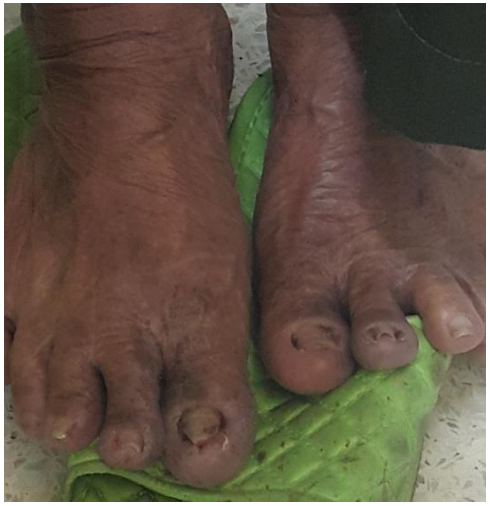
Table 2. Incidence of acneiform eruption with epidermal growth factor receptor (EGFR) inhibitors

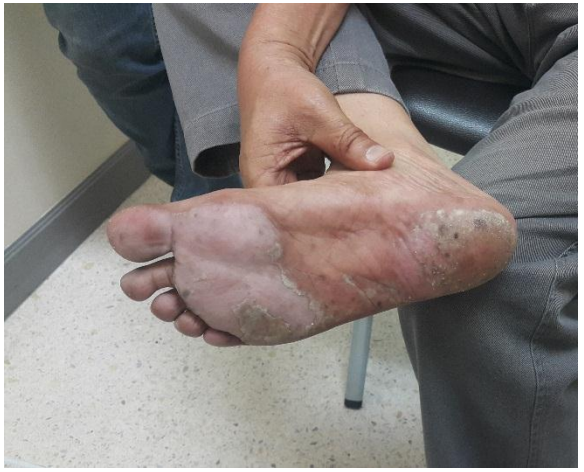
EGFR inhibitor	Any grade (%)	Grade 3 or 4 (%)
Cetuximab [14]		
Monotherapy	80	5.2
With irinotecan	80	9.3
Gefitinib		
50–100 mg/day [15]	53	65
150–1,000 mg/day [24]	1.6	2.2
Erlotinib [16, 113]		
150 mg/day	67–79	2.6–10.4
Panitumumab [36, 114]	70–100	10
Lapatinib [71]	38	3











MASCC™
Multinational Association Of Supportive Care In Cancer
www.mascc.org

Caring for Your Skin, Hair and Nails when on "Targeted Therapies"

"Targeted therapies" are a name for epidermal growth factor receptor inhibitors (EGFRIs). These types of drugs work in a number of cancers. They work by blocking cell processes that cancer cells need to survive. They hit a very specific set of cells in your body which is why EGFRIs are called "Targeted Therapies". Names of the most commonly used EGFRIs are:

- Erlotinib (Tarceva®)
- Cetuximab (Erbitux®)
- Panitumumab (Vectibix®)
- Lapatinib (Tykerb®)

Unfortunately, like other

What to LOOK for:

Acne-Like Rash:
An acne-like rash often begins 1-2 weeks after starting the drug. It may continue for many weeks and then slowly improve. It may look like acne but it is not acne and it will not improve with anti-acne medicines. The rash occurs most often on the face, neck, chest and back. The rash may cause discomfort or itching. For most people, the rash is mild to moderate and will not affect daily life. For some people, the rash is more severe and may make the person self-conscious about the way they look.

Dry Skin:
After a couple of months, you may notice that your skin looks dry and scaly. This may happen on your arms, legs or body. The dryness may be so severe that the skin on the fingertips and heels crack.

Itching:
Itching may start in the first few months of taking the drug. It may occur on the scalp, body, arms and legs. It also may itch where you have a rash or the skin is dry.

Nail Changes:
One of the later side effects of these drugs can be painful swelling and redness around the fingernails or toenails. Sometimes the nail area can become infected and require antibiotics.

Hair Changes:
After you are on the drug for awhile (usually over four months), your hair may change. Sometimes you can lose patches of hair or have hair thinning. On the other hand, you may also notice hair growing in areas such as the face. Eyelashes and eyebrows may grow very long. Long curling eyelashes may bother you and affect your vision.

What You Should Do to Prevent or Manage Side Effects:

General:
- Tell your doctor or nurse as soon as you have any

Itching:
- For itchy skin, use over-the-counter creams that

http://www.mascc.org/assets/documents/skin_toxicity_egfri_patientbrochure.pdf

Table 3. Different side effects of antiangiogenesis inhibitors

Side effect	Bevacizumab	Sorafenib	Sunitinib
Hypertension	+	+	+
Proteinuria	+	−	+
Thrombotic event	+	+	+
Bleeding	+	+	+
Gastrointestinal perforation	+	+	+
Wound healing	+	+	+
Fatigue	+	+	+
Mucositis	−	+	+
Diarrhea	−	+	+
Skin	−	Facial erythema, splinter subungual hemorrhage, ± alopecia	Hair depigmentation, splinter subungual hemorrhage, ± periorbital edema
Hand–foot reaction	−	+	+
Myelosuppression	−	+	+

From Perez-Soler R, Chachoua A, Hammond LA et al. Determinants of tumor response and survival with erlotinib in patients with non-small cell lung cancer. J Clin Oncol 2004;22:3238–3247, and Foon KA, Yang XD, Weiner LM et al. Preclinical and clinical evaluations of ABX-EGF, a fully human anti-epidermal growth factor receptor antibody. Int J Radiat Oncol Biol Phys 2004;58:984–990.

The Oncologist December 2007 vol. 12 no. 12 1443-1455

Targeted therapy: Cardiac side effects

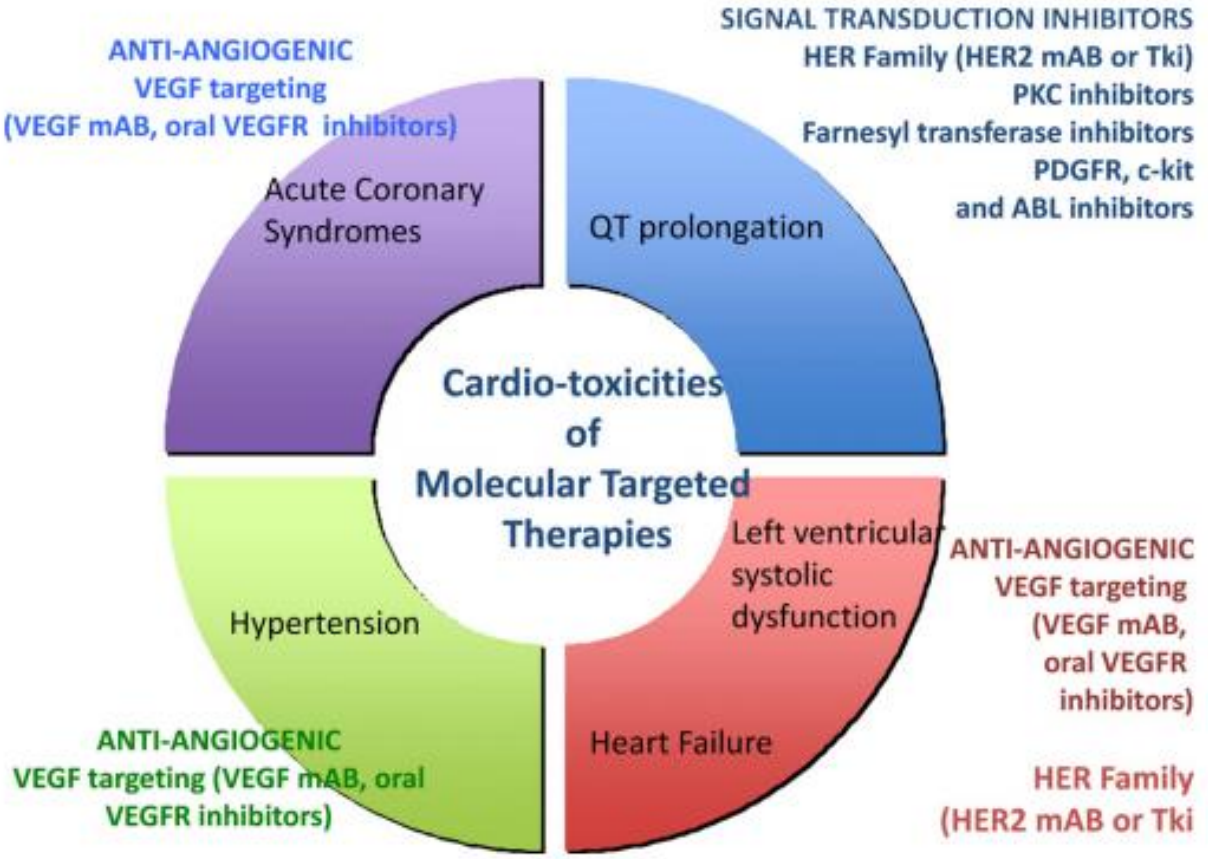


Fig. 1. Spectrum of cardiotoxicity associated with MTTs. Abbreviations: FTPase, farnesyl transferase protein; HER, human epidermal growth factor receptor; mAb, monoclonal antibody; MTT, molecular targeted therapy; PDGFR, platelet-derived growth factor receptor; PKC, phosphokinase C; TKI, tyrosine kinase inhibitor; VDA, vascular-disrupting agents; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Crit Rev Oncol Hematol. 2011 Dec;80(3):369-79

ENDOCRINE SIDE EFFECTS OF ANTI-CANCER DRUGS

Effects of anti-cancer targeted therapies on lipid and glucose metabolism

Bruno Vergès, Thomas Walter[1] and **Bertrand Cariou**[2]

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Email
bruno.verges@chu-dijon.fr

Table 3 Modification of plasma lipids and glycemia with mTOR inhibitors and tyrosine kinase inhibitors (TKIs).

	mTOR inhibitors	TKIs
Total cholesterol	↑	↔ (↓ in one study with imatinib)
Triglycerides	↑	↔ (↓ in one study with imatinib)
LDL cholesterol	↑	
HDL cholesterol	↔ or ↑	
Glycemia	↑	↑ or ↓

Eur J Endocrinol. 2014 Feb 1;170(2):R43-55

E2100 and AVF2119g— Grade 3-5 Adverse Events: Categories of Special Interest (%)

bevacizumab

Selected adverse events, Grade 3 - 5	E2100		AVF2119	
	PAC (n = 348)	PAC + AVA (n = 363)	Cape (n = 215)	Cape + AVA (n = 229)
Hypertension	1.4	16.0	0.5	20.0
Arterial thromboembolic events	0	3.6	0.5	0.4
Proteinuria	0	3.0	0	1.3
Hemorrhage	0.3	2.2	0.5	0.4
Left ventricular dysfunction	0.3	2.2	1.0	3.5
GI perforations	0	0.6	0	0
Neuropathy	18.1	25.3	0.9	0

WHICH SIDE EFFECTS OF PD1 ANTIBODIES?

- **Increased activity of the Immune System** may elicit auto-immune events

-Inflammations of the Colon with severe Diarrhea

-Pneumonitis with interstitial inflammatory infiltration

-Autoimmune inflammation of Thyroid or Pituitary or Adrenal Gland with hormonal deficiency

-neutropenia, thrombocytopenia or pancitopenia

-etc..

- **Low incidence but potentially fatal**: aggressive treatment with steroids or immunosuppressive drugs

Adverse Events Associated With Checkpoint Inhibitors Are Immune Related

irAE (All Grades), %	Ipilimumab + Dacarbazine[1] (n = 247)	Ipilimumab + Placebo[2] (n = 251)
Total	77.7	61.1
▪ Grade 3/4	41.7	14.5
Dermatologic		
▪ Pruritus	26.7	24.4
▪ Rash	22.3	19.1
Gastrointestinal		
▪ Diarrhea	32.8	27.5
▪ Colitis	4.5	7.6
Hepatic		
▪ Increase in ALT	29.1	1.5
▪ Increase in AST	26.7	0.8
▪ Hepatitis	1.6	0.8

1. Robert C, et al. N Engl J Med. 2011;362:2517-2526. 2. Hodi FS, et al. N Engl J Med. 2010;363:711-723.

Summary of CTLA-4 Blockade Immune-Mediated Toxicities

- Toxicity related to ipilimumab appears to be dose related
- Toxicity-related death occurred in < 1% of cases

Common (> 20%)

- Rash, pruritus
- Fevers, chills, lethargy
- **Diarrhea/colitis**

Occasional (3% to 20%)

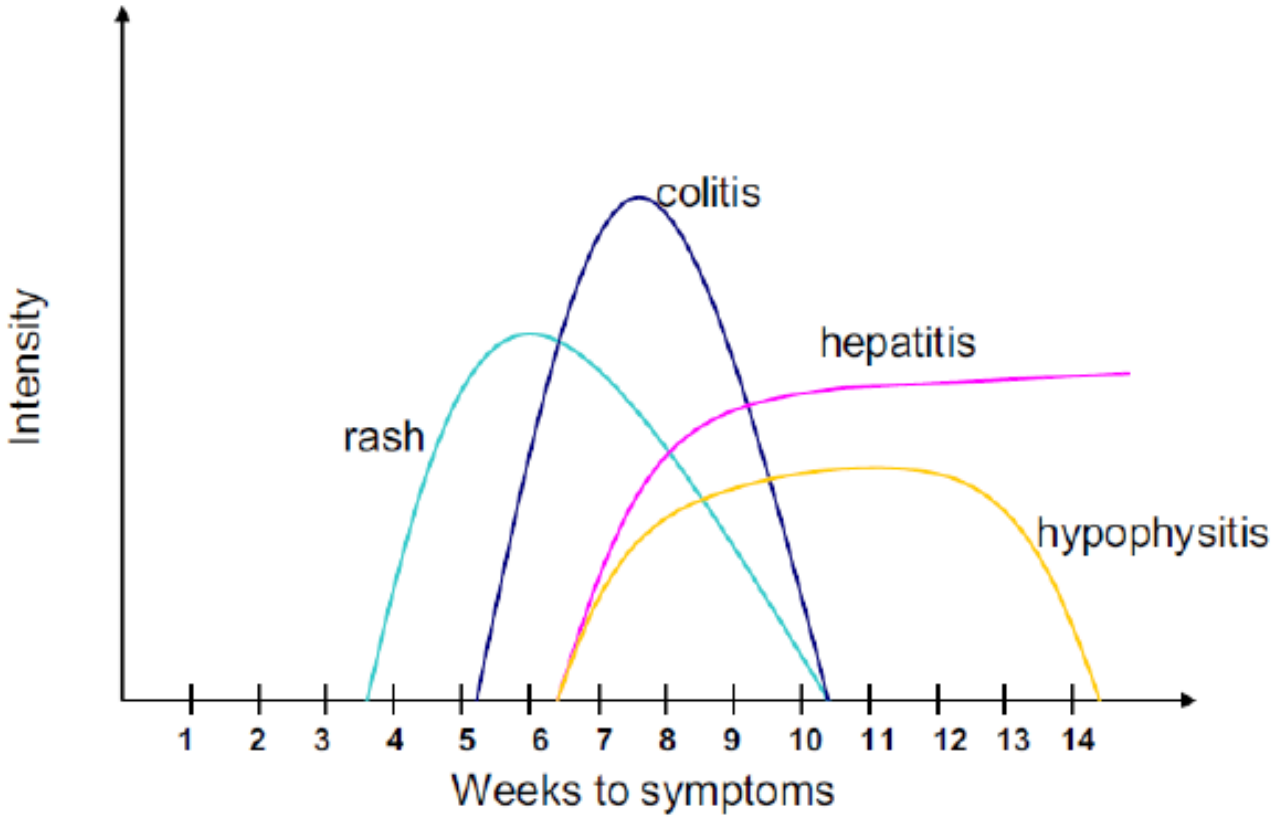
- Hepatitis/liver enzyme abnormalities
- Endocrinopathies: hypophysitis, thyroiditis, adrenal insufficiency

Rare (< 2%)

- Episcleritis/uveitis
- Pancreatitis
- Nephritis
- Neuropathies, Guillain-Barré, myasthenia gravis
- Lymphadenopathy (sarcoid)
- Thrombocytopenia
- Toxic epidermal necrolysis, Stevens-Johnson syndrome

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.
Weber JS, et al. J Clin Oncol. 2015;[Epub ahead of print].

Toxicity Patterns - Ipilimumab



Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

- Toxicity less common than with anti–CTLA-4 but can be fatal

Occasional (5% to 20%)

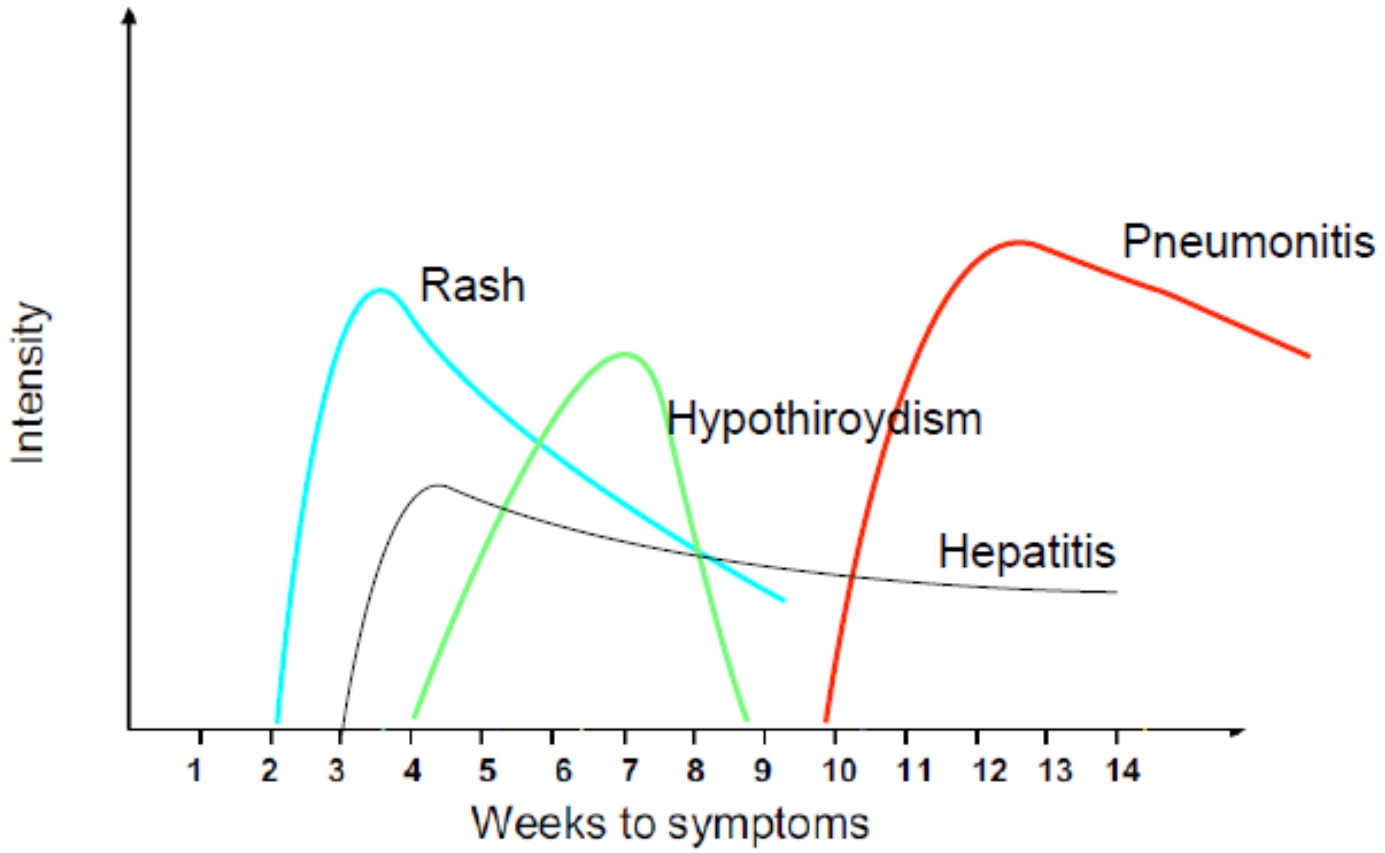
- Fatigue, headache, arthralgia, fevers, chills, lethargy
- Rash: maculopapular, pruritus, vitiligo
  - Topical treatments
- **Diarrhea/colitis**
  - Initiate steroids early, taper slowly
- Hepatitis, liver/pancreatic enzyme abnormalities
- Infusion reactions
- Endocrinopathies: thyroid, adrenal, hypophysitis

Rare (< 5%)

- **Pneumonitis**
  - Grade 3/4 toxicities uncommon
  - Low grade reversible with steroids and discontinuation
- Anemia

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697. Weber JS, et al. J Clin Oncol. 2015;[Epub ahead of print].

Toxicity Patterns - Anti-PD-1 Mab



Combination Therapy With Ipilimumab and Nivolumab: Toxicity Summary

- The safety profile of ipilimumab and nivolumab is characterized by immune related adverse events
- There is the potential for increased frequency of drug related adverse events with nivolumab combined with ipilimumab over either agent as monotherapy, in particular for lipase / amylase, AST / ALT
- Skin toxicity, uveitis, neurological, renal
- No new toxicities have been identified with the combination treatment
- Toxicities with the combination have been manageable and reversible following intervention with systemic steroids in alignment with established AE management algorithms

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European Society for Medical Oncology

How to manage irAEs – some general thoughts

- Almost all irAEs are reversible
- The grade of the AE depends on the patient's and the physician's reaction, and to a lesser extent on the compounds
- Fast identification – hit fast -> 24/7 Immune-Oncology (I-O) and Internist-Oncologist (I-O^2) expertise
- Start early immune suppression – hit early
- Do not hesitate to escalate – hit strong
- Consider to de-escalate – hit short

Awareness

Effective management is dependent on:

- Early recognition
- Appropriate monitoring
- Initiation of immunosuppressive therapy
- Patient education
- Utilization of treatment algorithms

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How to manage irAEs – compounds to use

- symptomatic: metoclopramide, loperamide, levothyroxine, cooling crème (aloe vera), steroid crème
- prednisolon 1-2mg/kg
- infliximab 5mg/kg, repeat after one week
- mycophenolate mofetil 1g bid
- tacrolimus 0,10-0,15mg/kg/day, split in 2 doses/day
- substitution of hydocortison 10-5-5 mg + fludrocortison 0,05-2mg/day, levothyroxine

General Management Algorithm

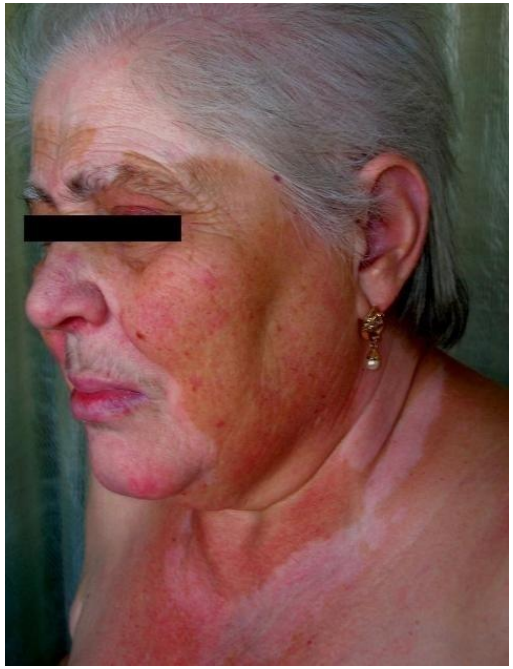
CTCAE grade	Management
1	• Supportive treatment • Increased monitoring of symptoms • Exclude infection • Patient education
2	As per grade 1 but in addition: • Withhold immunotherapy until toxicity has resolved to grade 1 or less • Consider oral steroids if persistent symptoms >5 days
3	• Supportive therapy • Commence intravenous steroids (typical dose 1–2 mg/kg methyprednisolone) • If not resolving within 48 h consider addition of other immunosuppressants (e.g. infliximab, mycophenolate) • Consider system specific investigations (e.g. colonoscopy) • Seek expert opinion of relevant specialist • Investigate and treat infection • Withhold immunotherapy, consider restarting if toxicity grade 1 or less on individual basis • Steroids will need to be tapered over 3–6 weeks
4	• As for grade 3 but permanently discontinue immunotherapy

Diarrhea

- G3-4 Diarrhea occurs in 7% of pts on ipilimumab and around 2% of pts on anti-PD-1 antibodies
- Colitis was observed in 5% of pts on ipilimumab (dose-dependent) and around 1.5% of patients on anti-PD-1 antibodies
- Grade 1 and 2 diarrhea should be managed with antidiarrheal medications, oral hydration and electrolyte supplements
- Persistent (>5 days) grade 2 diarrhea should be treated with oral steroids (0.5 mg/kg of prednisolone or equivalent)
- Grade 3-4 diarrhea should be treated with high dose intravenous steroids (methylprednisolone 1–2 mg/kg/day or equivalent) and consider further immunosuppresion (e.g infliximab, etc) if symptoms not improve within 2-3 days.
- Colonoscopy should be considered to assess ulceration and need for more aggressive immunosuppression (! risk of perforation)
- Steroids and infliximab are contraindicated if perforation is suspected

Skin Toxicity

- Rash (maculopapular), pruritus and occasionaly vitiligo and depigmentation
- Most common irAE with ipilimumab (40% any grade; 2% G3-4)
- Rash common with anti-PD-1 inhibitors (nivolumab > pembrolizumab)
- Grade 1 and 2 skin toxicity should be managed supportively with emollients, steroid creams (1% hydrocortisone) and topic or oral antihistamines.
- Grade 3 or 4 toxicity may manifest as Stevens-Johnson syndrome or toxic epidermal necrosis and requires evaluation by a dermatologist and treatment with iv high dose steroids



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REVIEW ARTICLE

Vitiligo-Like Depigmentation in Patients With Stage III-IV Melanoma Receiving Immunotherapy and Its Association With Survival: A Systematic Review and Meta-Analysis

Hansje-Eva Teulings, Jacqueline Limpens, Sophia N. Jansen, Aeilko H. Zwinderman, Johannes B. Reitsma, Phyllis I. Spuls, and Rosalie M. Luiten

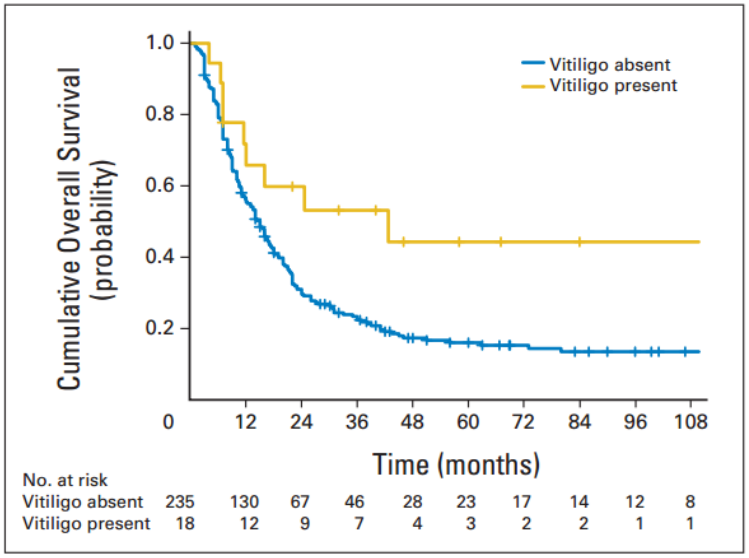


Fig 5. Overall survival in 253 patients receiving immunotherapy from 15 studies.

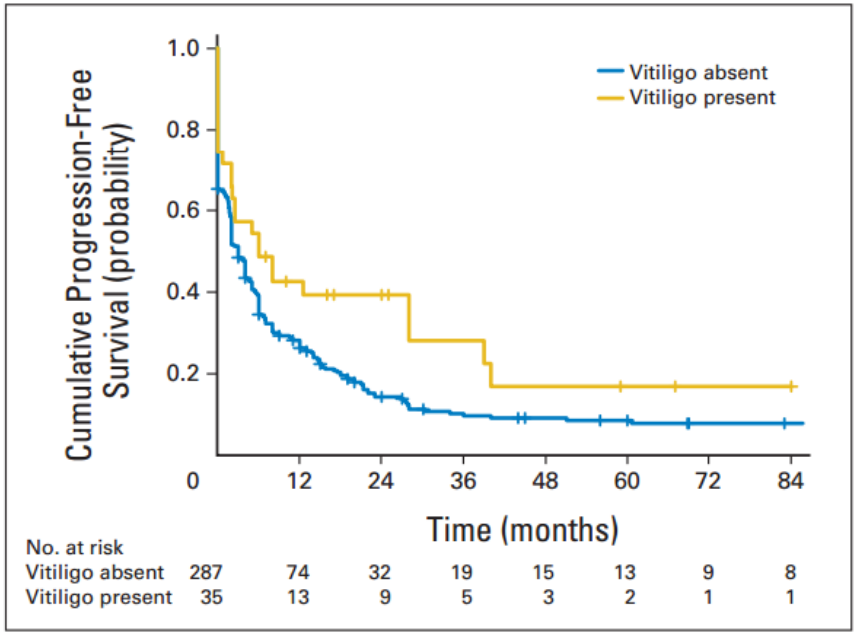


Fig 4. Progression-free survival in 322 patients receiving immunotherapy from 22 studies.

Hepatic Toxicity

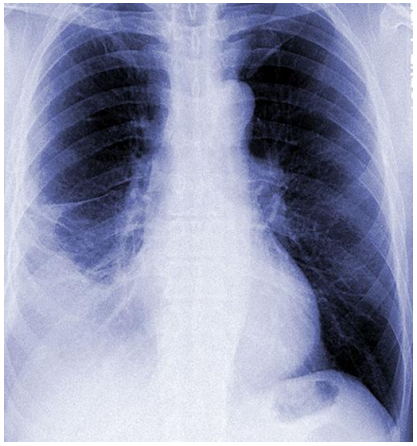
- Hepatotoxicity is reported in 3–9% of patients receiving ipilimumab and in 4– 10% of patients receiving anti-PD-1 antibodies, with grade 3 or 4 toxicity in 1%
- On biopsy hepatic inflammation with ballooning degeneration with diffuse lymphocytic infiltrates. Immunohistochemistrydemonstrated predominantly CD4+ cells in the periportal regions and CD8+ cells in hepatic lobules
- Exclude other causes (viral, disease, etc)
- Grade 1 and 2 hepatic toxicity requires close monitoring of the LFTs and in case of grade 2 hepatic toxicity persisting for more than 5-7 days intermediate dose steroids and liver biopsy should be considered
- Grade 3 or 4 should be treated with iv high dose steroids. If no improve within 48 h immunosuppression with mycofenolate mofitel should be considered.
- case report describes successful use of anti-thymocyte globulin in a patient with severe ipilimumab related hepatic failure

Endocrine Toxicity

- Endocrine toxicity can easily be overlooked, grade 1 endocrine irAE are asymptomatic and identified by routine testing
- Monitor of thyroid function tests recommended
- For ipilimumab, the most commonly reported endocrine toxicities are hypopituitarism, hypothyroidism and adrenal insufficiency; grade 3 or 4 toxicity occurred in <2%
- For anti-PD-1 antibodies the most commonly reported endocrine toxicity is thyroid dysfunction. Grade 3 or 4 toxicities in <1%
- Grade 1 or 2 endocrine toxicity may be monitored and hormone replacement therapy instituted where appropriate.
- Grade 3 or 4 toxicities requires hospitalization, institution of high dose iv steriods and review by an endocrinologist to direct hormone replacement.
- Patients with hypopituitarism may present with headache, fatigue and visual disturbance. Diagnosis is confirmed with pituitary dedicated MR imaging and assessment of pituitary hormones
- Endocrine damage is usually irreversible
- Once a patient's hormone replacement needs are addressed, immunotherapy can be resumed

Pneumonitis

- Rare with ipilimumab; it occurs in 9% of the patients on anti-PD-1 antibodies (3% grade 3 or 4)
- Grade 3-4 toxicities more common for pts who received thoracic radiotherapy or concurrent chemotherapy (up to 7%)
- Can present with dyspnea, cough, fatigue or respiratory failure
- Exclude other causes (! pts with lung cancer or pulmonary metastases)
- Grade 1 pneumonitis (asymptomatic radiological changes) may be monitored with no change in immunotherapy treatment. For grade 2 toxicity, immunotherapy therapy should be withheld and oral steroids commenced
- 17% of grade 2 pneumonitis can re-occur
- Grade 3 or 4 pneumonitis requires hospitalization, review by a respiratory physician, together with high dose intravenous steroids. If no benefit from steroids consider bronchoscopy to refine diagnosis and additional immunosuppression
- For grade 3 or 4 pneumonitis treatment should be permanently discontinued



What might impact the occurrence of AEs with immune checkpoint inhibitors?

- PD-L1 expression ✗
- Previous treatment with an immunotherapeutic agent ✓
- Atopic subjects ✓
- EGFR, ALK, BRAF, NRAS status ✗
- Dose, drug levels achieved ✓
- Combination with chemotherapy, radiotherapy or other immunotherapeutic agents ✓

Anti-PD-1 Monotherapy in Heavily Pretreated Patients with Advanced NSCLC: Summary of Safety

Agent	N	Safety Data
Nivolumab[1]	117	74% of patients experienced at least 1 TRAE; most common: fatigue (33%), decreased appetite (19%), asthenia (12%), and nausea (15%); 17% gr3-4 TRAEs: fatigue (4%), pneumonitis (3%), diarrhea (3%), and 2 treatment-associated deaths caused by pneumonia and ischemic stroke
Pembrolizumab[2]	495	71% of patients experienced at least 1 TRAE; most common: fatigue (19%), pruritus (11%), decreased appetite (10.5%), rash (10%); 9.5% gr 3-5 TRAEs: dyspnea (4%); pneumonitis (1.8%)- including one who died

1. Rizvi NA, et al. Lancet Oncol. 2015;16:257-265. 2. Garon E, et al. N Engl J Med 2015 Apr 19. [Epub ahead of print].

Less Common Immune-Related Adverse Events

- Hematologic (hemolytic anemia, thrombocytopenia)
- Cardiovascular (myocarditis, pericarditis, vasculitis)
- Ocular (blepharitis, conjunctivitis, iritis, scleritis, uveitis)
- Renal (nephritis)
- Several case reports of rare autoimmune-based toxicities in pts treated with ipilimumab
  - Lupus nephritis
  - Inflammatory enteric neuropathy
  - Tolsosa-Hunt syndrome
  - Myocardial fibrosis
  - Acquired hemophilia A
  - Autoimmune polymyositis

Ipilimumab adverse reaction management guide.

Toxicity Guidelines

- TFTs, CBCs, LFTs and metabolic panels should be obtained at each treatment and q6-12 wks for 6 mos posttreatment in all pts receiving checkpoint protein antibodies
- ACTH, cortisol should also be checked in pts with fatigue and nonspecific symptoms, plus testosterone in men
- Frequency of follow-up testing should be adjusted to individual response and AEs that occur
- Corticosteroids can reverse nearly all toxicities associated with these agents, but should be reserved for grade 3/4, or prolonged grade 2, irAEs

Weber JS, et al. J Clin Oncol. 2015;[Epub ahead of print].

Take home points

- educate pts
- exclude other causes: Infection
- Toxicity is mostly low grade
- start promptly i.v. steroids if G3-G4 toxicity
- The majority of both nivolumab and ipilimumab related AEs to date have been reversible and manageable by delaying study drug ± administration of corticosteroids; other immunosuppressants may also be needed
- Consider adding further immune-suppresant if symptoms do not resolve within 2-3 days from iv steroids or as steroid spare agents if pts on long term steroidal treatment or severe steroid-related AE
- Add immune-prophylaxis for opportunistic infections
- Taper down steroids slowly (risk of rebound)
- Monitor pts closely
- Seek expert advice


‘Here is a simple but powerful rule - always give people more than what they expect to get’
Nelson Boswell