

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Supportive Care and Management of Side Effects

Supportive Care and Management of Side Effects

- **Versions 2002–2018:**

**Albert / Bauerfeind / Brunnert / Bischoff / Costa / Dall /
Diel / Fersis Friedrich / Friedrich / Gerber / Göhring /
Hanf / Heinrich / Huober / Jackisch / Lisboa / Lück /
Lüftner / von Minckwitz / Möbus / Müller / Nitz /
Oberhoff / Rody / Schaller / Scharl / Schmidt / Schütz /
Solomayer / Souchon / Stickeler / Thomssen / Untch**

- **Version 2019:**

Harbeck / Schneeweiss

Content

- **Guidelines**
- **Assessment of toxicity**
- **Incidence of side effects (according technical product information; MedDRA-standard)**
- **Side effects according organ systems**
 - Incidence, prevention, therapy
- **Substance specific side effects**
 - Targeted drugs
- **Further issues**
 - Pain management, palliative care

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LEHREN
HEILEN

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■ Guideline - environment

Guideline Environment

Specific national and international guidelines deal with various aspects of evidence-based supportive therapy of cancer patients

Without claiming completeness, such guidelines will be quoted, with an emphasis on German guidelines.

Aspects concerning breast cancer patients will especially be highlighted.

The „Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG“ should especially be highlighted (<http://www.onkosupport.de>).

Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):

**S3-Leitlinie: Supportive Therapie bei onkologischen Patientinnen
Langversion 1.1 –April 2017 AWMF-Registernummer: 032/054OL**

- **Assessment of toxicity**
 - **Acute toxicity (NCI-CTCAE)**
 - **Long term toxicity (ICPC, ICD-GM)**

Assessment of toxicity

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Acute Toxicity (according to WHO¹ or NCI-CTC²)

Acute toxicities should be asked for and documented after every treatment course

LoE 5 D AGO ++

Grade

- 0 none
- 1 mild
- 2 moderate
- 3 severe
- 4 life threatening
- 5 death

Information required

- organs involved
- type of toxicity
- time interval after treatment
- effect on general health status
- treatment required
- recovery achieved

Long term toxicity (= secondary diseases after tumour therapy)

Long term surveillance and documentation in regular intervals (acc. ICPC³ following symptoms or acc. ICD-10-GM⁴ following diagnoses)

LoE 5 D AGO ++

Acute Toxicity (NCI CTCAE vs 5.0, 2017)

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- **Grade 1**
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**
Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- **Grade 3**
Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.**
- **Grade 4**
Life-threatening consequences; urgent intervention indicated.
- **Grade 5**
Death related to AE.

Activities of Daily Living (ADL)

- * Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- ** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- **Incidence of side effects
(according to technical product information by
MedDRA* classification)**

Chemotherapy – Acute Toxicities I

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DRUGS	SYSTEM ORGAN CLASS											
	INFECTIONS AND INFESTATIONS	NEOPLASMS BEN., ALIGNANT AND NSPECIFIED (INCL CYSTS & POLYPS)	BLOOD & YMPH. SYST. ISORDERS	IMMUNE YSTEM DISORDERS (ALLERGIES)	ENDOCRINE DISORDERS	METABOLISM AND NUTRITION DISORDERS	PSYCHIATRIC DISORDERS	NERVOUS SYSTEM DISORDERS	EYE DISORDERS.	EAR AND LABYRINTH DISORDERS	CARDIAC DISORDERS	VASCULAR DISOR. INCL HOT FLUSHES
<u>Alkylating antineoplastic agent</u>												
Cyclophosphamide	4	2	5	5	1	-	1	3	2	3	3	3
<u>Anti-Metabolites</u>												
Methotrexate	1	-	4	3	3	-	3	4	2	-	1	2
5-Fluorouracil*	5	-	5	2	2	5	-	3	3	-	5	3
Capecitabine	4	3 (Lipoma)	4	3	-	5	4	4	4	3	3	4
Gemcitabine	4	-	5	1	-	4	-	4	-	-	2	2
<u>Platinum-complexes</u>												
Cisplatin	4	2	5	3	2	5	-	4	2	5	4	4
Carboplatin	4	-	5	4	-	-	-	4	4	4	4	-
<u>Anthracyclines / Anthrachinones</u>												
Epi-/Doxorubicin	5	3	5	1-2	-	1-5	-	-	4	-	4	5
Liposom. Doxorubicin	5	-	5	-	-	5	3	4	(4)	-	4	4
PEG-lipos. Doxorubicin	4	-	4	-	-	5	-	4	4	-	4	-
Mitoxanthrone	5	3	5	3	-	4	-	4	3	3	4	3
<u>Taxanes</u>												
Paclitaxel	5	1	5	5	-	1	1	5	1	1	4	5
nab-Paclitaxel	4	-	5	3	-	5	4	5	4	4	4	4
Docetaxel	5	-	5	5	-	5	-	5	-	-	4	4
<u>Further tubulin-targeting drugs</u>												
Vinorelbine IV (PO)	5(5)	-	-(5)	2(-)	-	-	-(5)	-(5)	-(4)	-	2(3)	3(4)
Eribulin	4	-	4	-	-	5	4	5	4	4	4	4

Listing and grading of side effects was performed according the MedDRA-classification with the following categories of frequency: 1. Very rarely (<1/10,000); 2. rarely (≥ 1/1,000 to < 1/10,000); 3. occasionally (≥ 1/1,000 to < 1/100); 4. frequently (≥ 1/100 to < 1/10); 5. very frequently (≥ 1/10). - unknown (based on available data incidence not assessable)

Chemotherapy – Acute Toxicities II

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	SYSTEM ORGAN CLASS										
DRUG	RESPIRAT., HORAC. & MEDIA- STINAL DIS.	GASTROINT.DISOR D. (NAUSEA, EMESIS)	HEPATOBIARY DISORDERS	SKIN & SUBCUT. TIS. DISORD. (ALOPECIA)	MUSCULOSKELETA L & CONNECTIVE TISSUE DISORDERS	RENAL& URINARY DISORDERS	PREGN., PUERPER. & PERINATAL CONDIT.	REPRODUCT. SYS. & BREAST DISORDERS	GENERAL DISORD. & ADMINI- STRATION SITE CONDITIONS	CONGEN., FAMILIAL GENET. DISORDERS	SPECIAL FEATURES
Alkylating antineoplastic agent											
Cyclophosphamide	2	4	4	5	-	5	-	4	5	-	Hyponatraemia
Anti-Metabolitee											
Methotrexate	4	5	5	4	3	3	-	3	1	-	Mucositis, risk of “third space”-toxicity
5-Fluorouracil	5	5	3	5	-	-	-	-	5	-	Risk DPD-deficiency: light 5%, severe 0,1%; diarrhea, heart
Capecitabine	4	5	4	5	4	3	-	3	5	-	Hand-foot-syndrome (HFS), risk of DPD-deficiency; heart
Gemcitabine	5	5	5	5	4	5	-	-	5	-	Flu-like symptoms, edema, heart
Platinum-complexes											
Cisplatinum	4	5	4	4	-	5	-	3	5	-	Nephrotoxicity, ototoxicity, CIPN
Carboplatin	4	5	-	4	4	4	-	-	4	-	Colitis (nephrotoxicity)
Anthracyclines / Anthrachinones											
Epi-/Doxorubicin	2	5	-	5	1	4		1	5	-	Cardiotoxicity (CHF), sec. malign. diseases, extravasation
Lipo. Doxorubicin	4	5	4	5	4	3	-	(4)	5	-	
PEG-lipo. Doxo.	4	5	-	5	4	-	-	4	5	-	Palmar and plantar erythema (PPE)
Mitoxanthrone	4	5	3	5	-	3	-	3	4	-	Sec. AML, cardiomyopathy
Taxanes											
Paclitaxel	2	5	1	5	5	-	-	-	5	-	Peripheral neuropathy (CIPN); hypersensitivity, myalgia
nab-Paclitaxel	4	5	3	5	5	3	-	3	5	-	Peripheral neuropathy (CIPN)
Docetaxel	5	5	-	5	5	-	-	-	5	-	Fluid retention, paronychia, colitis, myalgie
Further tubulin-targeting drugs											
Vinorelbine IV (PO)	3(4)	2 (5)	5(4)	2(5)	-(4)	2(4)	-	-	-	-	Phlebitis, GI-Tox (PO), CIPN
Eribulin	5	5	4	5	5	4	-	-	5	-	Constipation, CIPN

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Endocrine Therapy – Toxicities

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SERM												
Tamoxifen	-	3	4	-	3	5	-	4	4	-	-	4
AI												
Anastrozole	-	-	-	-	-	4	5	5	4	-	4	5
Exemestane			4			4	5	4				5
Letrozole	3	-	3	-	-	5	4	4	3	-	3	5
SERD												
Fulvestrant	4	-	3	4	-	4	-	4	-	-	-	4

DRUG	RESPIR., THORAC. & MEDIASTIN. DIS.	GASTROINT. DIS. (NAUSEA, EMESIS)	HEPATOBIILIARY DISORDERS	SKIN & SUBCUT.TIS. DIS. (ALOPECIA)	MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS	RENAL & URINARY DISORDERS	PREGN., PUERPER. & PERINAT. COND.	REPRODUCT. SYS. & BREAST DISORDERS	GENERAL DIS. & ADMINISTRATION SITE CONDITIONS	CONGEN., FAMIL. & GENET. DISORD.	SPECIAL FEATURES
SERM											
Tamoxifen	3	5	4	5	4	-	-	5	5	1	Hot flushes; rarely: endometrial Ca (>55y); thrombosis
AI											
Anastrozole	-	5	4	5	5	-	-	5	5	-	Hot flushes, arthralgia, osteoporosis; cognition
Exemestane		5		5	5				5	-	Hot flushes, arthralgia, osteoporosis; cognition
Letrozole	3	4	3	5	5	3	-	4	5	-	Hot flushes, arthralgia, osteoporosis; cognition
SERD											
Fulvestrant	-	5	5	4	4	4	-	3	5	-	Hitzewallungen

Listing and grading of side effects was performed according the MedDRA-classification with the following categories of frequency:

1. Very rarely (<1/10,000); 2. rarely ($\geq 1/1,000$ to < 1/10,000); 3. occasionally ($\geq 1/1,000$ to < 1/100); 4. frequently ($\geq 1/100$ to < 1/10); 5. very frequently ($\geq 1/10$).

- unknown (based on available data incidence not assessable)

Side effects according Organ Systems

Incidence, Prevention, Therapy

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1. Infections and infestations

- General prophylaxis for infections
- Hepatitis B virus screening

Prophylaxis of Infections

rarely applicable to patients with solid tumors (e.g. BC)

ASCO Practice Guideline „Antimicrobial Prophylaxis...” 2013

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- **Avoidance of highly infection-risking behavior or situations**
- **Prophylactic treatment in low risk patients**
- **Prophylactic treatment in high risk* patients (e.g. according to NCCN Guidelines) with**
 - **Antibiotics**
 - **Anti-fungal agents (triazole)**
 - **Virostatics in solid tumors**
 - **Granulocyte colony-stimulating factors**

Oxford		
LoE	GR	AGO
5	D	+
1a	B	-
1a	A	++
1a	B	+/-
5	D	-
1a	A	++

* High risk: estimated duration of neutropenia < 100/ μ l > 7d

Hepatitis B virus screening before chemotherapy

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Oxford		
LoE	GR	AGO

- Hepatitis B virus screening before adjuvant chemotherapy (HBsAG, anti-HBC)

2c B +

In case of positive serology or reactivation:

- Interruption of chemotherapy
- Prophylactic therapy with virustatic drugs if HBV-DNA detected (according AGIHO/DGHO – recommendations)

5 D ++

1b A ++

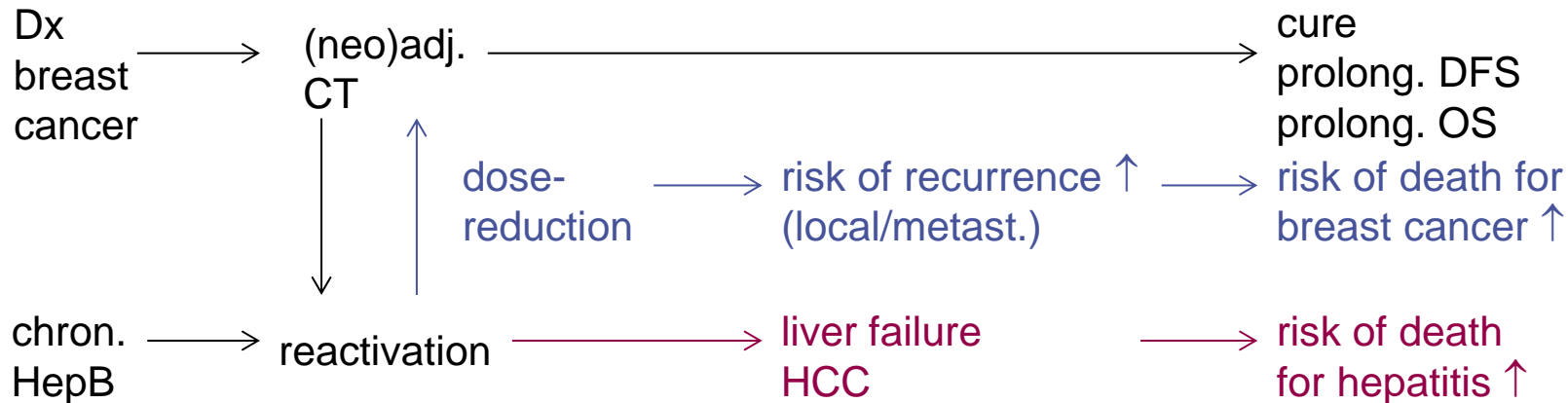
- Hepatitis C virus screening before chemotherapy

5 D +/-

Interaction Hepatitis B and Tumour Therapy

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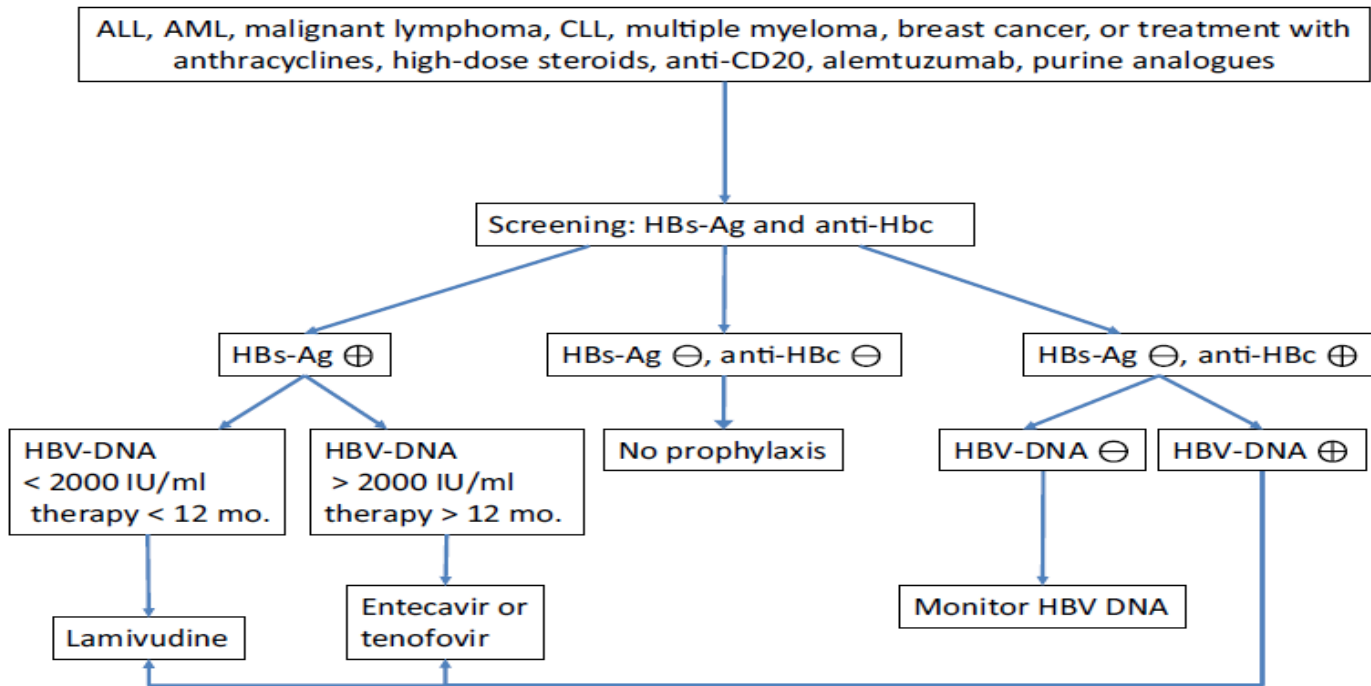
„Number needed to screen“ in Germany:

Prevalence 0.5%-1% (general population):	100 to 200
Prevalence 3.6% (migrants):	28

AGIHO / DGHO – recommendations on Hepatitis B virus screening in oncology

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International recommendations on Hepatitis B virus screening

Recommendations of Various Authoritative Bodies Regarding Screening for Hepatitis B to Mitigate the Risk of HBV Reactivation

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Organization	Recommendation	Tests to Be Done
Centers for Disease Control and Prevention	Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders	HBsAg, anti-HBc, anti-HBs
American Academy of Dermatology	Hepatitis B reactivation after treatment with tumor necrosis factor inhibitors has been reported; in the appropriate clinical setting, patients should be screened for hepatitis B infection.	Not stated
American Association for the Study of Liver Diseases	All patients before beginning immunosuppressive therapy	HBsAg, anti-HBc
Asian Pacific Association for the Study of the Liver	Before receiving immunosuppression or chemotherapy, patients should be screened for HBsAg. Patients who are going to receive biologic agents such as anti-CD20 or anti-tumor necrosis factor- α should be screened for anti-HBc.	HBsAg, anti-HBc
European Association for the Study of the Liver	All candidates for chemotherapy and immunosuppressive therapy should be screened.	HBsAg, anti-HBc
American Society of Clinical Oncology	Physicians may consider screening patients belonging to groups at heightened risk for chronic HBV infection or if highly immunosuppressive therapy is recommended.	Consider HBsAg, consider anti-HBc
US Preventive Services Task Force	Screen persons who are immunosuppressed.	HBsAg

Side Effects According Organ Systems

Incidence, Prevention, Therapy

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2. Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Secondary Malignancies I

Oxford
LoE GR

- With regard to solid tumors, chemotherapy induced secondary malignancies are rare events
- Alkylating agents increase the risk of leukemia dose-dependently to a total of 0.2–0.4 % within 10 - 15 years
- Anthracycline-containing regimens increase the risk of MDS and leukemia to 0.2–1.7 % within 8 to 10 years
- PARP-inhibitors are associated with an increased risk of AML and MDS to 0.5-1%
- Radiotherapy increases the risk of leukemia by 0.2–0.4% in patients treated with anthracycline-containing chemotherapy
- Tamoxifen approximately doubles the risk for developing endometrial cancer (in pts. older than 55 at start of therapy)

2a

2a

2a

2b

2b

2b

Secondary Malignancies II (After Radiotherapy)

Oxford
LoE

- Radiotherapy (PMRT, BET) may moderately enhance the risk of ipsilateral lung cancer and angiosarcoma (10-15 / 10.000) 5–10 years after treatment
 - Enhanced risk especially among ever smokers
 - No difference of secondary malignancy between PBI und WBI

1a

2b

2c

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3. *Blood and Lymphatic System Disorders*

- Anemia
- Neutropenia
- Febrile Neutropenia (FN)

Anemia – Indications for Therapy with Erythropoiesis-stimulating agents (ESAs)

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- Indicated in asymptomatic anemia
- Therapy and secondary prophylaxis in CT-induced anemia
 - In the adjuvant setting
 - In the neoadjuvant/metastatic setting
- In dose-dense / dose-escalated adj. CT (iddETC)
- Treatment start at Hb-levels < 10 g/dL
- Target Hb 11–12 g/dL
- Improvement of outcome (DFS, OS)
- Risk of thromboembolic events is increased by use of ESAs

Oxford		
LoE	GR	AGO
1a	B	-
1a	A	+
1b	A	+
1a	A	+/-
1b	A	+
1a	A	+
1a	A	+
1a	B	--
1a	A	

Phase III Study of Epoetin Alfa Versus Best Standard of Care in Anemia Patients with Metastatic Breast Cancer

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N=2.098 Pat., Hb <11g/dl; non inferiority study.

Prespecified upper non inferiority margin = 1.15

	PFS (median)		OS (median)	ORR	RBC transfusions	TVE
Epo	Invest.* 7,4 Mon	IRC** 7,6 Mon	17,2 Mon	50%	5,8%	2,8%
BSC	7,4 Mon.	7,6 Mon.	17,4 Mon	51%	11,4%	1,4%
	HR: 1,09	HR: 1,02	HR: 1,06	OR: 0,95	p<.001	p=.04
	Upper CI: 1,20	Upper CI: 1,146				

* Investigator determined

** Independent review committee

Practical Use of ESAs

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- **Epoetin α and Darbepoetin are equieffective**
- **Dosage:**
 - Epoetin α : 150 IU/kg 3 x weekly s.c. or
40.000 IU 1 x /week s.c. or
80.000 IU q2w s.c. or
120.000 IU q3w s.c.
 - Epoetin β : 30.000 IE weekly s.c.
 - Darbepoetin: 2,25 μ g/kg s.c. weekly or 500 μ g s.c. q3w
- **Weekly hematologic blood controls**
 - Dose reduction if Hb-increase > 1g/dl within 2 weeks
 - Dose increase if Hb-increase < 1g/dl within 4-6 weeks
- **In case of FID (“functional iron deficiency”) iron supplementation, preferably i.v.**
- **Stop ESA-treatment if there is no Hb increase after 9 weeks**

Granulocyte Colony-stimulating Factors

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	Oxford		
	LoE	GR	AGO
■ Primary prophylaxis for expected febrile neutropenia (FNP)			
■ If expected risk for FNP 10–20%	1b	B	+/-
■ In case of individual risk factors	3b	C	+
■ If expected risk for FNP >20% (e.g. DAC, dose-dense CT)	1a	A	++
■ Secondary prophylaxis during chemotherapy (previous FNP or neutropenia grade IV > 7 days)	1b	A	++
■ Therapeutic usage for FNP	1a	A	+/-
■ Start related to chemotherapy and duration			
■ Pegfilgrastim day 2	1b	A	++
■ Lipegfilgrastim day 2	1b	A	++
■ Filgrastim/Lenograstim from day 2–3 until ANC > 2–3 x 10 ⁹	1b	A	++

Management of Febrile Neutropenia

c.f. Recommendations by Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO)
www.dgho-infektionen.de (H. Link et al: 04/07)

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Definition (oral temperature of $>38.5^{\circ}\text{C}$ or two consecutive readings of $>38^{\circ}\text{C}$ for 2 h in a patient with an ANC of $<500\text{ cells/mm}^3$ or expected to fall to $<500\text{ cells/mm}^3$)

	Oxford		
	LoE	GR	AGO
■ Clinical examination	5	D	++
■ Daily evaluation	5	D	++
■ Hospitalization of high risk patients	1b	A	++
■ Homecare in low risk patients	1b	A	+
■ Differential blood count	5	D	++
■ Blood cultures	5	D	++
■ Imaging of lungs	3	C	++
■ Immediate initial empiric antibiotic therapy	1a	A	++
■ Empiric antifungal therapy 4–7d in case of failure of antibiotic therapy	1b	A	++
■ G-CSF for treatment (not prophylactic)	2b	B	+/-

Empirical Antibiotic Therapy

The recommendations for empirical antibiotic therapy are currently changing because of infection biological findings.

Current recommendations should be referred to regularly and adjusted to within personal professional judgement.

The “Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de” is a source for regular consultation.

EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment

Step 1: Assess frequency of FN associated with the planned chemotherapy regimen

FN risk $\geq 20\%$

FN risk 10-20%

FN risk $< 10\%$

Step 2: Assess factors that may increase the risk of FN:

High risk: Age > 65 years

Increased risk: (level I and II evidence)
Advanced disease
History of prior FN
No antibiotic prophylaxis

Other Factors: (level III and IV evidence)
Poor performance (ECOG > 1)
Female gender
Haemoglobin < 12 g/dL

Step 3: Define the patient's overall FN risk for planned chemotherapy regimen

Overall FN risk $\geq 20\%$

Overall FN risk $< 20\%$

Prophylactic G-CSF recommended

G-CSF prophylaxis not indicated

Reassess at each cycle

Side Effects According Organ Systems

Incidence, Prevention, Therapy

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4. Endocrine disorders

Therapy-associated Amenorrhea (CRA, CIA, TIA)

**Oxford
LoE**

- **CRA may be permanent or temporary (depending on age of the patient and type of chemotherapy)**
- **The risk of CRA increases with patient's age and duration of the chemotherapy**
- **CRA is an imperfect surrogate for menopause and fertility**
- **Adjuvant endocrine therapy with GnRHa induces reversible amenorrhea, but delays conception to a less fertile period**
- **Ovarian reserve of women who remain premenopausal after CTX is reduced**
- **CRA is associated with improved outcome (DFS/OS)**

2b

2b

5

5

2b

1b

Synonym: Chemotherapy related or induced / Treatment induced Amenorrhea (CRA, CIA, TIA)

Side Effects According Organ Systems

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5. Psychiatric Disorders

- Depression
- Fatigue
- Cognitive impairment
- Sleep disturbances

(Therapy Associated) Depression

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- Depression is an often reported adverse event in breast cancer patients (20–30%)
- Psychological interventions are effective to improve mood, but not survival in distressed and depressed patients
- Antidepressants have shown to improve depression in breast cancer patients
- Regular exercise participation can prevent depression among breast cancer survivors

Oxford		
LoE	GR	AGO
2a	B	
1b	A	
1b	A	
2b	B	+

(Therapy Related) Fatigue

Oxford		
LoE	GR	AGO
2a	B	
1a	A	++
1a	A	++
1b	D	+
2b	B	+
1a	D	+

- Fatigue frequently present in breast cancer patients (30–60%)
- Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue
- Psycho-social interventions specifically addressing fatigue are efficient in reducing fatigue
- Physical exercise can improve fatigue
- Diet, Yoga can improve fatigue
- Methylphenidate can improve fatigue

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(Therapy Associated) Cognitive Impairment

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	Oxford	
	LoE	GR
■ Therapy-related cognitive deficits (“chemobrain”) frequently described (16–75%)	2a	B
■ Cognitive-behavioral therapy is beneficial for cognitive function	2b	B
■ Methylphenidate might improve cognitive function in patients with cancer	3a	C
■ Under therapy with aromatase inhibitors, deterioration of cognitive performance was observed (espec. verbal memory)	1a	B

(Therapy Associated) Sleep Disturbances

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- Sleep disturbances are a common problem of breast cancer patients during and after therapy (20–70%)
- Behavioral therapies demonstrated efficacy in the treatment of insomnia and improved the quality of life

Oxford		
LoE	GR	AGO
2a	B	
1b	A	++

Side Effects According Organ Systems

Incidence, Prevention, Therapy

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6. Nervous system disorders

- **Chemotherapy-Induced Peripheral Neuropathy (CIPN)**

Chemotherapy-Induced Peripheral Neuropathy (CIPN)

- **Incidence with taxanes:**
 - Grade 1–2: 20–50 %
 - Grade 3–4: 6–20 %
 - **Risk factors: type and dose of chemotherapy, BMI, reduced physical activity**
 - **Individual risk factors**
 - Diabetes mellitus
 - Nutritive-toxic compounds part. alcohol
 - Renal failure
 - Hypothyreosis
 - Collagenoses / vasculitis
 - Vitamine deficiency
 - HIV-Infection
 - CMT-Gen mutations
- Unclear:
- Other genetic factors (SNPs, mutations)

Chemotherapy-induced Peripheral Neuropathy

– Prevention –

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Oxford		
LoE	GR	AGO

Non drug-based prevention

- Functional training (physical fitness, sensomotoric stimulation training etc.)
- Compression treatment (tight surgical gloves, compression stockings)
- Cooling gloves and stockings
- Elektro-acupuncture

5	D	+
2b	B	+
2b ^a	B	+/-
1b	B	-

Drug-based prevention

- Venlafaxine
- Palmitoylethanolamine (PEA) topically or PO
- A-lipoic-acid (thioctic acid), amifostine, amitriptyline, acetyl-L-car-nitine, carbamazepine, electrolyte solutions, glutathione, Goshajinkigan (GJG), oxcarbazepine, vitamine B, vitamine E or other compounds¹

2a	C	+/-
5	D	+/-
1b	A	-

¹ A list of no recommended drugs at Hershman et al. 2014

Chemotherapy-induced Peripheral Neuropathy

– Therapy –

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Non drug-based therapy

- **Functional training (physical fitness, sensomotoric stimulation training etc.)**
- **Physiotherapy / physical treatment**

Drug-based therapy

- **Menthol locally (1%), capsaicin/lidocain locally**
- **Baclofen/amitryptiline/ketamin-gel**
- **Duloxetine for therapy of CIPN.induced pain**
- **Opioids for therapy of CIPN.induced pain**
- **Palmitoylethanolamine (PEA) topically or PO.**
- **Venlafaxine**
- **Gabapentin, pregabalin**
- **Amitryptiline/ nortriptyline, imipramine/desipramine**
- **Acetyl-L-carnitine, lamotrigine or other compounds¹**

Oxford		
LoE	GR	AGO
2a	C	+
5	D	+
5	D	+
2b	B	+
1b	B	+
5	D	+
5	D	+/-
5	D	+/-
1b	B	+/-
1b	B	+/-
1b	B	-

¹ A list of no recommended drugs at Hershman et al. 2014

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7. Cardiac Disorders

Cardiotoxicity as Long-term Side Effect

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	Oxford		
	LoE	GR	AGO
▪ Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m ² cum. dose, resp.)	2b	B	
▪ Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity	1b	B	
▪ Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:	2b	B	
▪ Elderly patients			
▪ Obesity			
▪ Hypertension			
▪ Hypercholesterolemia			
▪ Pre-existing cardiac diseases (incl. borderline LVEF)			
▪ Diabetes mellitus			
▪ Monitoring of cardiac function:			
▪ Standardized echocardiography (LVEF or SF in %)	3b	C	+
▪ Troponin I as marker of cardiac toxicity	2b	B	+/-
▪ Betablocker-prophylaxis during anthracycline therapy	2a	B	+/-

Adjuvant Trastuzumab

Cardiac Monitoring for CHF

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Oxford LoE: 5

GR: D

AGO: ++

Before start of trastuzumab

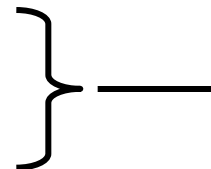
- History, physical examination (edema, hepatomegaly)
- Echocardiography (alternative to MUGA)

} **Assessment
of LVEF**

During trastuzumab

Regular assessment of

- Heart rate increase > 15% above individual base level
- Body weight increase ≥ 2 kg/week
- Cardiac signs and symptoms



3 monthly assessment of LVEF

Feasibility of Treatment Combinations Considering Toxicities

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Regarding cardiac toxicity

- Trastuzumab simultaneous to radiotherapy
- Trastuzumab simultaneous to epirubicin
- Trastuzumab simultaneous to doxorubicin
- Anthracycline simultaneous to radiotherapy

Regarding lung and breast fibrosis

- Tamoxifen simultaneous to radiotherapy
- Chemotherapy simultaneous to radiotherapy

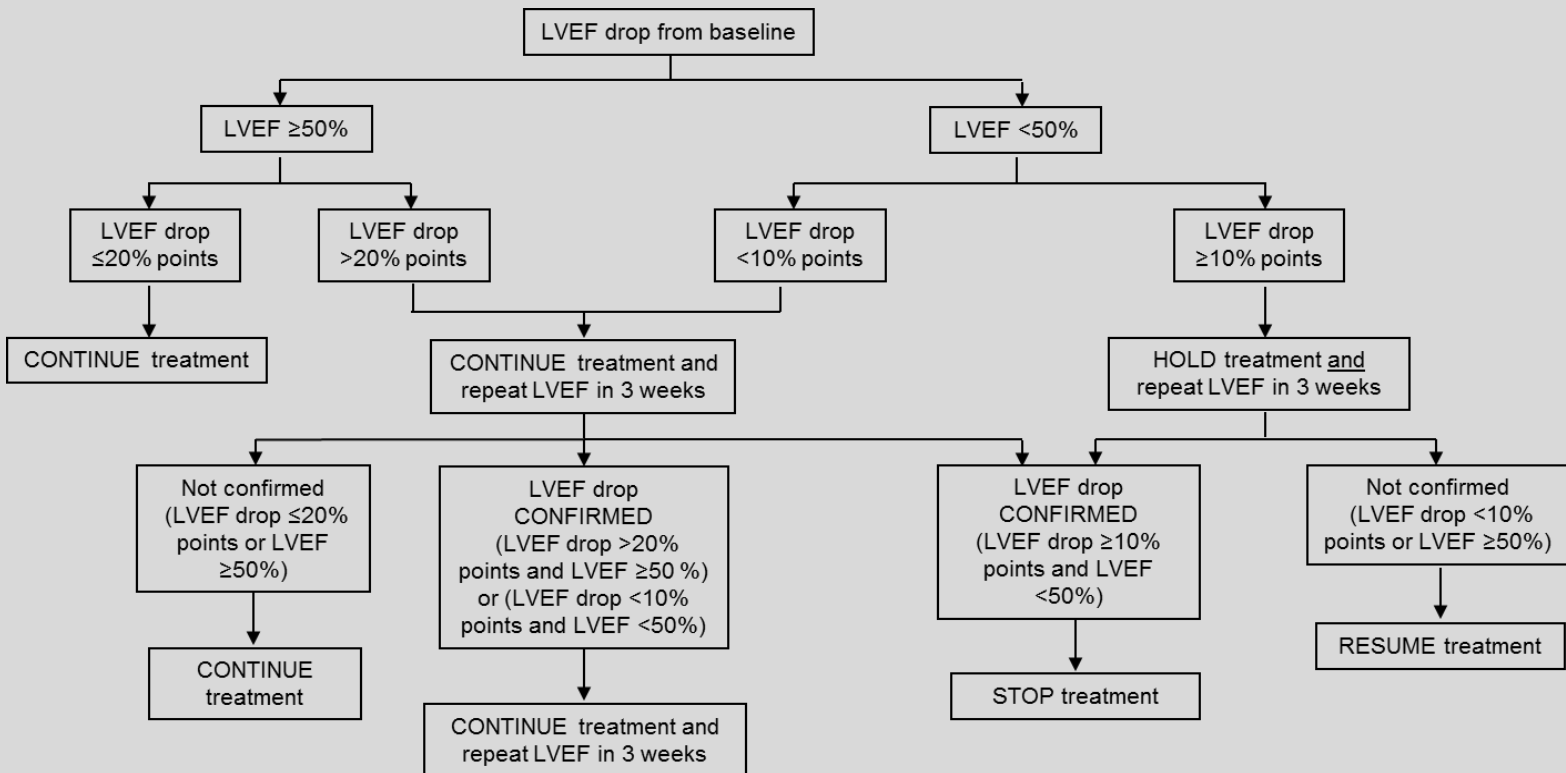
Oxford		
LoE	GR	AGO
2b	B	+
2b	B	+/-
2b	B	-
2c	C	-
3	C	+/-
1b	B	-

Side Effects of Trastuzumab/Pertuzumab:

Algorithm in Case of Cardiac Toxicity

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8. Gastrointestinal Disorders

- Nausea, Emesis
- Mucositis
 - Stomatitis (Everolimus)
- Diarrhea
- Constipation

Antiemetic Therapy

<http://www.mascc.org/antiemetic-guidelines>

www.onkosupport.de

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- **After assessment of emetic potential of chemotherapy protocol**
- **Neurokinin-1-receptor-antagonists**
- **Dexamethasone**
- **5-HT₃-antagonists**
- **Fixed antiemetic combination therapy**
- **Rescue Medication**
 - Olanzapine
 - Levomepromazine, benzodiazepines
 - Cannabinoids, ginger

Oxford		
LoE	GR	AGO
5	D	++
1b	A	++
1a	A	++
1b	A	++
1b	A	++
3b	C	+

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Antiemetic Therapy

<http://www.mascc.org/antiemetic-guidelines>

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Emetogenes Risiko (Risiko ohne Antiemese zu erbrechen)		Akute Phase (vor der medikamentösen Tumorthherapie)					Verzögerte Phase (ab 24 h nach der medikamentösen Tumorthherapie)	
Hoch > 90 %	hoch emetogen und AC- basierte Chemotherapie bei Patienten mit Mammakarzinom	5-HT ₃ -RA					-	
		NK ₁ -RA					1	
		Dexamethason					Dexamethason Tag 2-4	
Moderat 30-90 %	carboplatinhaltige Chemotherapie ³	5-HT ₃ -RA					-	
		NK ₁ -RA („kann“)					1	
		Dexamethason					fakultativ Dexamethason Tag 2-3	
	moderat (außer Carboplatin)	5-HT ₃ -RA					-	
		Dexamethason					2	
Gering 10-30 %		Dexamethason	oder	5-HT ₃ -RA	oder	MCP	-	
Minimal < 10 %		Keine Routineprophylaxe					Keine Routineprophylaxe	

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Supportive Therapy

Antiemetics

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Wirkstoffgruppe	Substanz	Dosierung	Nebenwirkungen	Potenzial
Serotonin- antagonisten	Ondansetron Tropisetron Granisetron Palonosetron	8 mg i.v., 2 x 4-8 mg p.o. 5 mg i.v., 5 mg p.o. 1-3 mg i.v. 0, 25 mg i.v.	Kopfschmerzen, Diarrhoe, Flushsymptomatik Transaminasenanstieg Darmatonie in hoher Dosierung	sehr hoch
NK1-Antagonisten	Aprepitant Fosaprepitant Rolapitant	125 mg d1, 80 mg d 2-3 p.o. 150 mg d1 i.v. 180 mg d1 p.o.	Cytochrom-P-450- Aktivierung mit Dosis-reduktion von Dexamethason (2 x 8 mg). Keine Kombination mit Astemizol, Terfenadin, Cisaprid	sehr hoch
Dopamin- antagonisten/ substituierte Benzamide	Metoclopramid Alizaprid	bis zu 120 mg/24h als Dauerinfusion od. als Tropfen bis zu 300 mg i.v. oder p.o./24 h (6 Amp. od. 6 Tbl.)	Dyskinesien (Antidot: Biperiden) Angstreaktion, Depressionen, Diarrhoe	hoch
Phenothiazine/ Butyrophenone	Haloperidol	1-3 mg 4 x/d	Sedation, Senkung der Krampfschwelle, transiente Leberwerterhöhung	mäßig
Corticosteroide	Dexamethason Prednisolon	8-20 mg i.v. 1-3 x/d 100-250 mg i.v. 1-3 x/d	Blutzuckerentgleisung, psychotische Reaktionen, Flush, Blutdruckanstieg	mäßig
Benzodiazepine	Diazepam Lorazepam	bis zu 20 mg/d 0,5-1,0 mg/d	Sedation, Atemdepression	gering
NEPA (Netupitant and Palonosetron)	fixe Kombinations partner (oral)	NE 300 mg PA 0,5 mg		sehr hoch

Mucositis Prevention

[http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006\(dtV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006(dtV).pdf)

Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):

„Supportive Therapie bei onkologischen Patientinnen – interdisziplinäre Querschnittsleitlinie“, released 11.11.2016

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Standardized mouth hygiene for prophylaxis of oral mucositis should be adhered to by all age groups and during all cancer-related therapies with any risk for oral mucositis. 	2b		++

This entails:

1. Patient:
 - Regular mouth washs (H₂O, NaCl)
 - Soft tooth brushes
 - Interdental care: flossing or using interdental brush
 - Avoidance of alcohol, tobacco, hot food, sour food
 - Regular screening for lesions
2. Risk adjusted prophylaxis by dentist
3. Continuous clinical control

There is no evidence with regard to the use of one of the following compounds: allopurinol, capsaicin, glutamine, honey, camomile, camomile oil or extract, chewing gum, kefir, methadone, nystatin, pentoxifylline, povidone-iodine, vitamine A/E/combinations

Prevention of Everolimus-Induced Stomatitis Using Dexamethasone Mouthwash

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- **Study design: single arm phase II-trial (SWISH)**
- **Cohort: 92 pts., treated with everolimus 10 mg and exemestane 25 mg**
- **Schedule: 10 mL of alcohol-free dexamethasone 0.5 mg per 5 mL oral solution (swish for 2 min and spit) for at least 8 weeks**
- **Results: after 13 wks exposition all-grade incidence of stomatitis 27% (BOLERO 67%),
≥ grade 2 events 9% (BOLERO 27%)**

Mucositis

[http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006\(dtV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006(dtV).pdf)

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- **Desinfecting / antiphlogistic measures :**
Mouth rinsing with infusions of chamomile or salvia, extracts of chamomile, etheric oils, polyvidon-iodine, hexetidine. Local therapy with crystal violet solution 0.5% or tinctura myrrhei, H. mometasonfuroate + propylene glycol
- **Mucosa protecting measures (during / after application of chemotherapy):**
Sucking ice cubes (especially from pineapple juice) during 5-fluorouracile- or HD-melphalane. Calcium folinate (Leucovorin-mouth gel®) every 4–6 hrs for HD-methotrexate:
do not start earlier than 24 hours after end of MTX-Infusion (otherwise potential loss of efficacy of MTX!).
Dexpanthenole (Panthenol®-Solution. 5%) mouth rinsing.
- **Local antimycotic treatment:**
Amphotericin B, nystatin, fluconazole
- **Local antiviral treatment**
Aminoquinuride / tetracaine-HCl , Aciclovir®
- **Local anaesthesia:**
Benzocaine, Doxepin 0,5% p.o.
- **Pain Therapy:** Opioids if indicated

Diarrhea

- **Adsorbent agents**
 - Carbo medicinalis; *caoline / pectine, Al-Mg-silicate hydrate*
- **Analgetics, opioids**
 - Loperamide; *codeine, morphine IV, tintura opii (tinture of opium), butylscopolamine*
- **Pseudomembranous colitis**
 - Metronidazole *or (if not effective) vancomycin*

Constipation

Important Side Effect of Opioid Treatment

- **Bulging agents**
 - Psyllium, flaxseed (shredded)
- **Osmotic laxatives**
 - Macrogol > Lactulose (Cochrane review **LoE 1a, AGO +**)
 - Oral radio-opaque material: ultima ratio e.g. sodium amidotrizoate
 - Sorbitol
- **Motility stimulating laxatives**
 - Senna, Ricinus (Castrol Oil), Bisacodyl, sodium-picosulfate
- **Emollients** (Internal lubricants e.g. paraffin)
- **Opioid-receptor-antagonists**
(in opioid-related constipation)
 - Methylnaltrexone

Side Effects According Organ Systems

Incidence, Prevention, Therapy

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9. Skin & Subcutaneous Tissue Disorders (Alopecia)

Skin toxicities

Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):
„Supportive Therapie bei onkologischen PatientInnen – interdisziplinäre
Querschnittsleitlinie“, released 11.11.2016

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- **Avoidance of chemotherapy-induced alopecia by cooling the patient's scalp***
- **Prophylaxis of hand-foot-syndrome using urea containing lotions (5-10%)**
- **Prophylaxis of nail changes and hand-foot-syndrome by cooling hands during application of docetaxel**

Oxford		
LoE	GR	AGO
1b		+/-
1b		+
2b		+

Scalp Cooling: Scalp Cooling Alopecia Prevention Trial (SCALP) and metaanalyses

AGO: +/- LOE 2b B

- Nangia J, Wang T, Osborne C, et al. Effect of Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer: The SCALP Randomized Clinical Trial JAMA. 2017 Feb 14;317(6):596-605.

Primary Outcome: hair preservation

Cooling: 50.5 % success vs. 49.5 % failure

Non-cooling: 0 % success vs. 100 % failure

Fisher's exact test $p < 0.001$

Zwei Metaanalysen: AGO: +/- LOE 1b

- Scalp cooling reduced relative risk (RR) of alopecia by 43% (RR, 0.57; 95% CI, 0.45-0.72; $I^2 = 11\%$; $P < .00001$). (Rugo & Voigt, Clinical Breast Cancer 2018; 18(1): 19-28.)
- Incidence rate of scalp metastasis (SC vs. no-SC) 0.61% vs. 0.41%; $P = 0.43$. (Rugo & Voigt; BCRT 2017)

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10. MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS

(see Chapter Osteooncology)

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11. General Disorders & Administration Site Conditions

Extravasation of Potentially Necrotizing Compounds (Anthracyclines, Taxanes, Vinorelbine)

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- **Dexrazoxane for treatment of anthracycline-extravasations
(exception: liposomal Anthracyc.)**
- **Hyaluronic acid for treatment of taxane/
vinorelbine-extravasations**

Oxford		
LoE	GR	AGO
2b	B	++
3b	D	++

Extravasation of Chemotherapy

Role of Dexrazoxane/Hyaluronic Acid

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Dexrazoxane for treatment of anthracyclines paravasates

Day 1: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs

Day 2: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs

Day 3: 500 mg/m² (max. 1000 mg), IV 1–2 hrs

Otherwise or if treatment with dexrazoxane is not indicated, following measures are recommended:

1. Local cooling: ice packs for 15 min every 6 hrs, for at least 3 days, alternatively: 24 h continuous ice cooling
2. Local application (with swab) of dimethylsulfoxid 99% (DMSO) every 3-4 hours for at least 3 days (better 14 days), allow it to air dry. The interval may be extended to 6 hours from day 4 onward.

Hyaluronic Acid in case of Taxan/Vinorelbin Paravasates:

- 1-10 Amp a 150 IU
- 1 ml dissolvent (z.B. NaCl 0.9%)
- Local anaesthesia
- No thermotherapy after taxanes
- Dry warmth 4 x daily 20 min during vincaalkaloids

- **Substance-Specific Side Effects**
 - **Antibodies and Antibody-Drug-Conjugates (ADC)**
 - **CDK 4/6-Inhibitors**
 - **PARP-Inhibitors**
 - **Small molecules (TKI, mTOR.Inihibitor)**
 - **Immun-Checkpoint-Antibodies**

Kex-Toxicities – Antibodies and Antibody-Drug-Conjugates (ADC)

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Oxford		
LoE	GR	AGO

Trastuzumab

- Cardiotoxicity in the adjuvant setting (1,0–2,0%)
- Troponin I might identify patients who are at risk for cardiotoxicity

1b A

2b B

Pertuzumab

- Skin rash, diarrhea, mucositis

1b A

Trastuzumab-Emtansine (T-DM1)

- Thrombocytopenia, hepatotoxicity pyrexia, headache, pneumonitis, neuropathy

1b A

Bevacizumab

- Hypertonus, proteinuria, bleeding, left ventricular dysfunction,

2b B

Toxicities of New Substances – CDK 4/6 Inhibitors (Palbociclib/Ribociclib/Abemaciclib)

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UE, %	All Grades	Grade 3	Grade 4
Neutropenia	79,5/ 74,3 /41,3	56,1/ 49,7 /19,6	10,4/ 9,6 /1,5
Leukopenia	39,0/ 32,9 /20,8	24,1/ 19,8 /7,3	0,7/ 1,2 /0,3
Anemia	24,1/ 18,6 /28,4	5,2/ 0,9 /5,8	0,2/ 0,3 /0
Thrombocytopenia	15,5/ 5,7 /10,0	1,4/ 0,6 /2,0	0,2/ 0 / <1,0
Fatigue	37,4/ 36,5 /40,1	1,8/ 2,1 /1,8	0/ 0,3 /0
Nausea	35,1/ 51,5 /38,5	0,2/ 2,4 /0,9	0/ 0 /0
Vomiting	15,5/ 29,3 /28,4	0,5/ 3,6 /1,2	0/ 0 /0
Diarrhea	26,1/ 35,0 /81,3	1,4/ 1,2 /9,5	0/ 0 /0
Alopecia	32,9/ 33,2 /26,6	-	-
Exantheme	17,8/ 17,1 /14,0	0,9/ 0,6 / <1,0	0/ 0 /0
ALT elevated	9,9/ 15,6 /15,6	1,7/ 7,5 /5,8	0,1/ 1,8 /0,3
AST elevated	9,7/ 15,0 /15,0	2,5/ 4,8 /3,0	0/ 0,9 /0
Infections	60/ 50,3 /39,1	6,0/ 3,6 /4,0	1/ 0,6 /0,9
QT-prolongation	N.A./ 7,5 /N.A.	N.A./ 3,0 /N.A.	N.A./ 0 /N.A.
Palbociclib/ Ribociclib /Abemaciclib			

QT interval prolongation: Ribociclib vs Placebo

- **Post-baseline QT interval prolongation > 480 msec 6.9% vs 1.2% (incidence Ribo vs Placebo)**
- **Post-baseline QT interval prolongation > 500 msec 1.5% vs 0.3%**
- **Therapy discontinuation for QT interval prolongation 0.3% vs 0.6%**
- **QT interval prolongation is not associated with symptoms; however, QT interval prolongation stands for elevated risk of life-threatening arrhythmia *“torsades de pointes”* (TdP)**

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Toxicities of new compounds: mTOR-Inhibitor

– Everolimus –

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UE, %	All grades (%)	grade ≥ 3 (%)
Stomatitis	11,6	1,6
Exanthema	7,4	0,02
Anemia	3,3	1,3
Fatigue	6,8	0,8
Nausea	5,6	0
Emesis / Vomiting	2,9	0
Diarrhea	6,2	0,02
Loss of appetite	6,0	0,02
Headache	3,9	0
Weight loss	3,9	0
Dyspnea	3,8	0,08
Arthralgia	3,3	0
Epistaxis	3,1	0
Edema	2,9	0
Constipation	2,6	
Pyrexia	2,9	0
Cough	4,5	0
ALT Elevated	2,6	0
Pneumonitis	0,2	0
Asthenia	2,4	0,04
Dysgeusia	4,3	0

Toxicities of new compounds: PARP-Inhibitors

– Olaparib, Talazoparib –

Olaparib

AE. %	all grades (%)	grade ≥ 3 (%)
AE, overall	97.1	36.6
Neutropenia	27.3	9.3
Anemia	40.0	16.1
Fatigue	28.8	2.9
Nausea	58.0	0
Emesis	29.8	0
Diarrhea	20.5	0.5
Appetite loss	16.1	0
Headache	20.0	1
Pyrexia	14.1	0
Cough	17.1	0
ALT elevated	11.2	1.5
AST elevated	9.3	2.4
PPE	0.5	
Treatm. discontinuation	4.9	

Talazoparib

AE. %	all grades (%)	grade ≥ 3 (%)
AE, overall	98,6	31,8
neutropenia	34,6	20.9
Anemia	52.8	39,2
Fatigue	50,3	1,7
Nuasea	48,6	0,3
Emesis	24,8	2,4
Diarrhea	22,0	0,7
Appetite loss	21,3	0,3
Headache	32,5	1,7
Back pain	21,0	2,4
Dyspnea	17,5	2,4
Pleural effusion	2,1	1,7
PPE	1,4	0,3

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Toxicities of new compounds: antiHER2-TKI

– Neratinib, Lapatinib –

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Lapatinib

AE, %	All grades	Grade ≥ 3
Diarrhea	61%	6%
Nausea	18%	4%
Rash	60%	6%
Fatigue	16%	4%
Cardiac	3%	< 1% SAE
Hepatobiliary	8%	
All AE %	92%	SAE 6%

Neratinib

AE, %	Alle Grade	Grad ≥ 3
Diarrhea	90	40,1
Nausea	43	2
Abdominal pain	36	2
Fatigue	27	2
Emesis	26	3
Exanthema	18	0,6
Stomatitis	14	0,6
Appetite loss	12	0,2
Dyspepsia	10	0,4
ALAT elevated	9	1,2
ASAT elevated	7	0,7
Nail disorders	8	0,3
Dry skin	6	0

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Primary Prophylaxis with loperamide

LoE

2b

AGO

B

++

Immune Checkpoint Inhibitors

- **Therapeutic approaches (antibodies)**

- **PD1 /PD-L1**

- PD1**

- **nivolumab**
 - **pembrolizumab**

- PDL1**

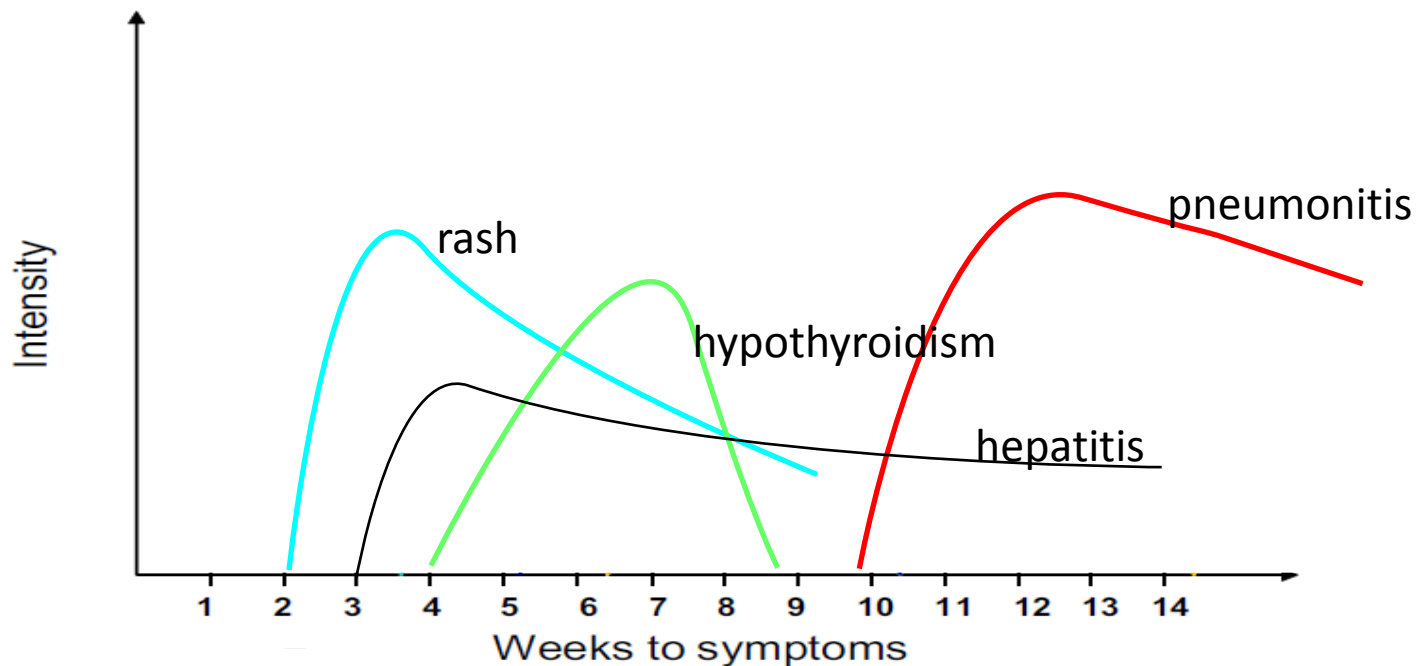
- **atezolizumab**
 - **durvalumab**
 - **avelumab**

Immune Checkpoint Inhibitors

Time Course of Adverse Events, ex. Nivolumab

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Haanen J et al. Ann Oncol 2017; 28 (suppl 4): 119-142

Immune Checkpoint Inhibitors

– side effects –

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■ Adverse events \geq grade 3

- diarrhea
- fatigue
- skin lesions (maculopapular exanthema, vitiligo, epidermolysis)
- pneumonitis
- colitis
- hypophysitis
- hepatitis
- nephritis
- thyreoiditis (hyper-/hypothyroidism)
- Guillain-Barré syndrome
- cardiomyopathy
- myopathy – myalgia – rhabdomyolysis
- uveitis

Immune Checkpoint Inhibitors

Toxicities (Total in %)

	atezolizumab	nivolumab	pembrolizumab
diarrhea	18.6%	13%	18%
colitis	1.1%	2%	1%
exanthema	18.6%	15%	<1%
hepatotoxicity	0.3%	1%	0.5%
hypophysitis	<0.1%	<1%	0.5%
pneumonitis	3.1%	3%	2.9%
thyroid dysfunction	hyper- 1.7% hypo- 4.7%	hyper -1% hypo- 4%	hyper- 1.2% hypo- 8.3%
nephritis	<1%	1%	0.7%
neuropathy	0.2%	<1%	<1%

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Atezolizumab technical product information 2018, Nivolumab, safety management BMS 2014, Pembrolizumab PI 2014

Immune Checkpoint Inhibitors

Principles of Adverse Event Management

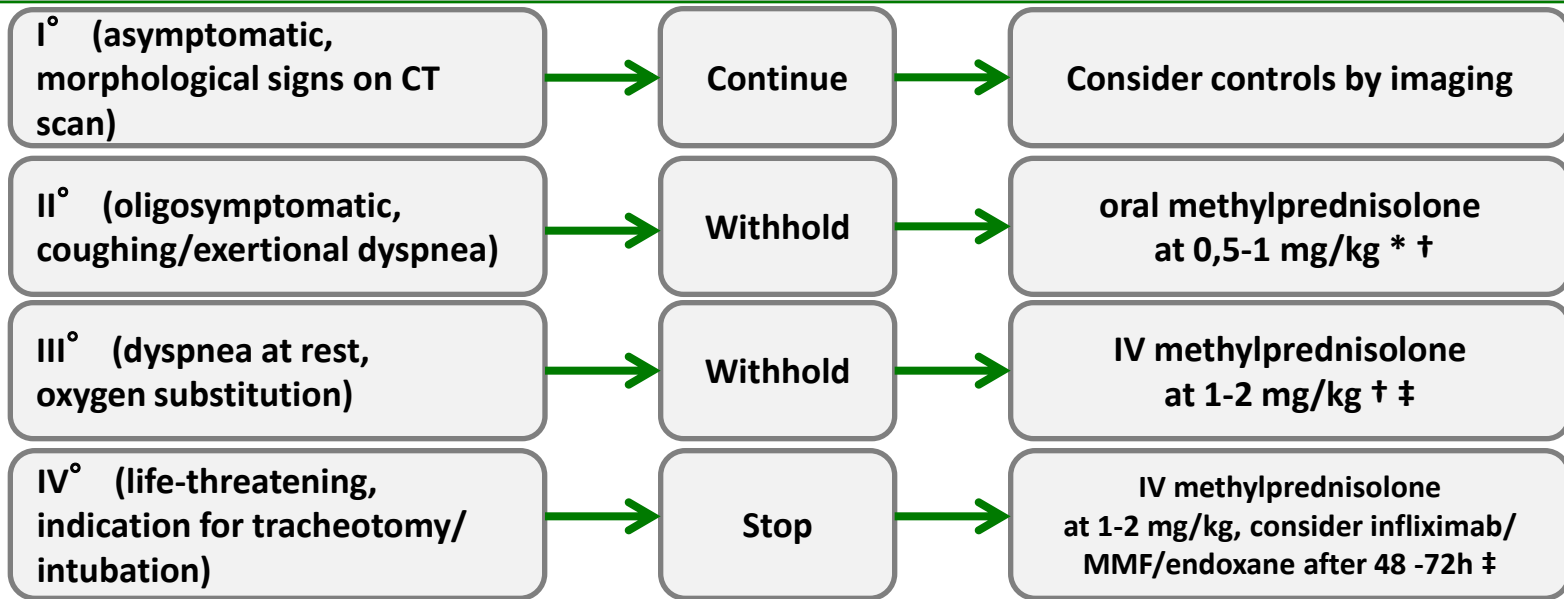
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CTC AE-Grade	Management
1	<ul style="list-style-type: none"> supportive therapy close examination exclusion of infective complications patient information
2	<p>Like grade 1 but</p> <ul style="list-style-type: none"> intermission of therapy until recovery of all irAE to grades 0-1 consider corticosteroids
3	<ul style="list-style-type: none"> supportive therapy IV steroids (e.g. 1-2 mg/kg prednisolone) <p>In case of no improvement within 48 h:</p> <ul style="list-style-type: none"> consider additional immunosuppressive therapy (infliximab, MMF) consider further organ specific diagnostics (eg. colonoscopy) consider specialists consultations exclusion or treatment of infection stop of treatment, re-initiation after recovery to CTC AE grades 0, 1 slow reduction of steroids (3-6 weeks)
4	Like grade 3 but persistent withdrawal of therapy

Management of Pneumonitis

PD1/ PDL1 Inhibitors



* Prophylactic antibiotic therapy with ciprofloxacin 500 mg bid orally, ulcus prophylaxis with PPI, oral substitution of potassium. In case of no improvement, treat like for pneumonitis III°

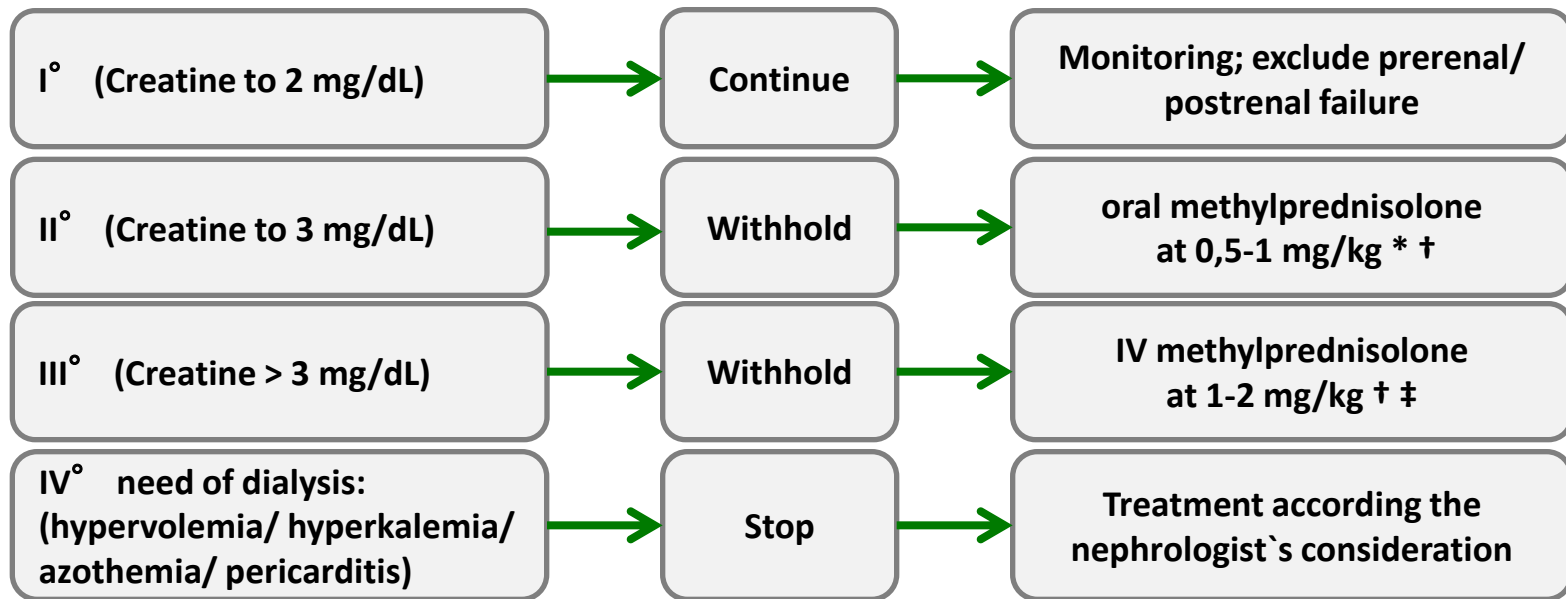
† in case of improvement reduce steroids over 1 month

‡ > pneumonitis III° bronchoscopy plus lavage / consider biopsy

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

Management of Nephritis

PD1/PDL1-Inhibitors



* Prophylactic antibiotic therapy with ciprofloxacin 500 mg bid orally, ulcer prophylaxis with PPI, oral substitution of potassium. In case of no improvement treat like for nephritis III°

† in case of improvement reduce steroids over 1 month

‡ > nephritis III° refer to nephrologist for biopsy

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

Management of Hypophysitis

PD1/PDL1-Inhibitors

TSH/ft3/ ft4 suppressed
 +/- hyperkalemia
 +/- hypoglycemia
 +/- hypotension
 +/- fatigue
 -> susp. autoimmune
 hypophysitis/central M.
 Addison

**ACTH †, cortisone in serum,
 24h-urine: cortisone, PRL †,
 IGF-1 †, FSH/ LH
 (premenopause), ECG, vital
 signs followed by MRI of the
 pituitary gland‡**

**methylpredisolone
 1-2 mg/kg IV*!
 Further hormone
 substitution
 (L-thyroxin) based on
 endocrinologist`s
 recommendation**

† ACTH: adrenocorticotrophic hormone, PRL: prolactin, IGF-1: insulin growth factor-1

‡ MRI of the pituitary gland

* Prophylaktisch antibiotic therapy with ciprofloxacin 500 mg bid orally, ulcus prophylaxis with PPI, oral substitution of potassium

! Under reduction of methylprednisolone (cave: reduced bioavailability of oral steroids) to levels of 8 mg/d orally
 -> switch to hydrocortisone as maintenance (15-10-5 mg daily);
 no ACTH controls

Addison emergency card via Department of Endocrinology; ->in stress situations (fever, deterioration of general condition) triple dose to 45-30-15 mg daily

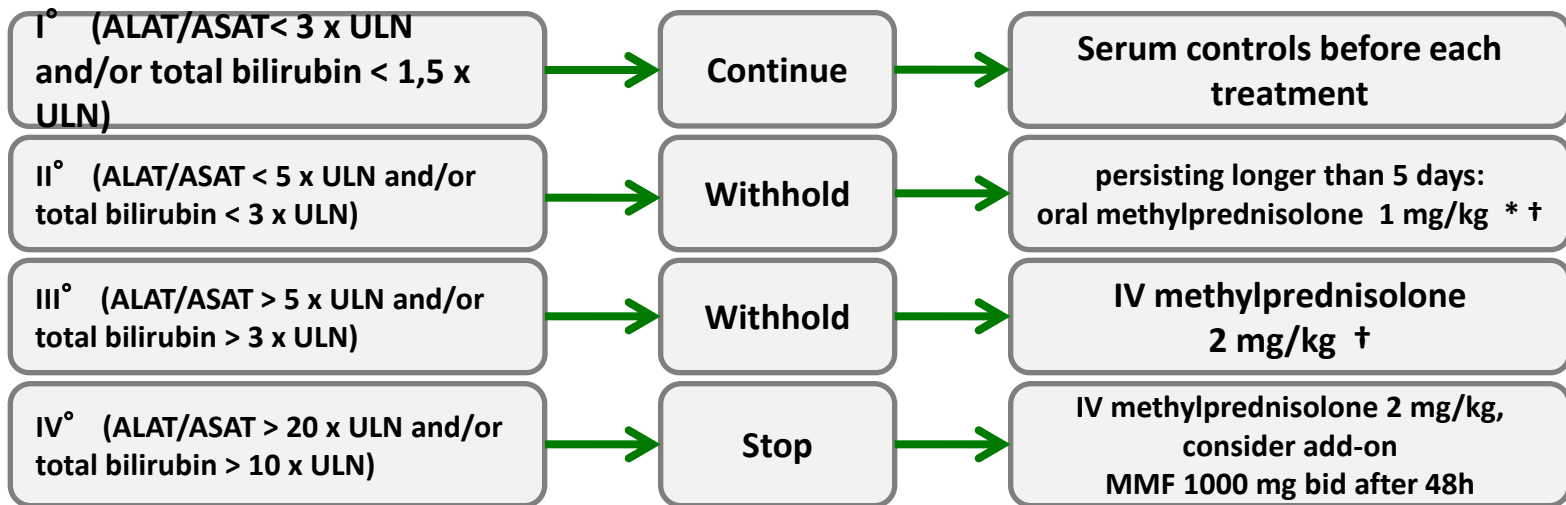
Consider treatment with checkpoint inhibitors at clinical discretion

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

Management of Hepatitis PD1/PDL1-Inhibitors

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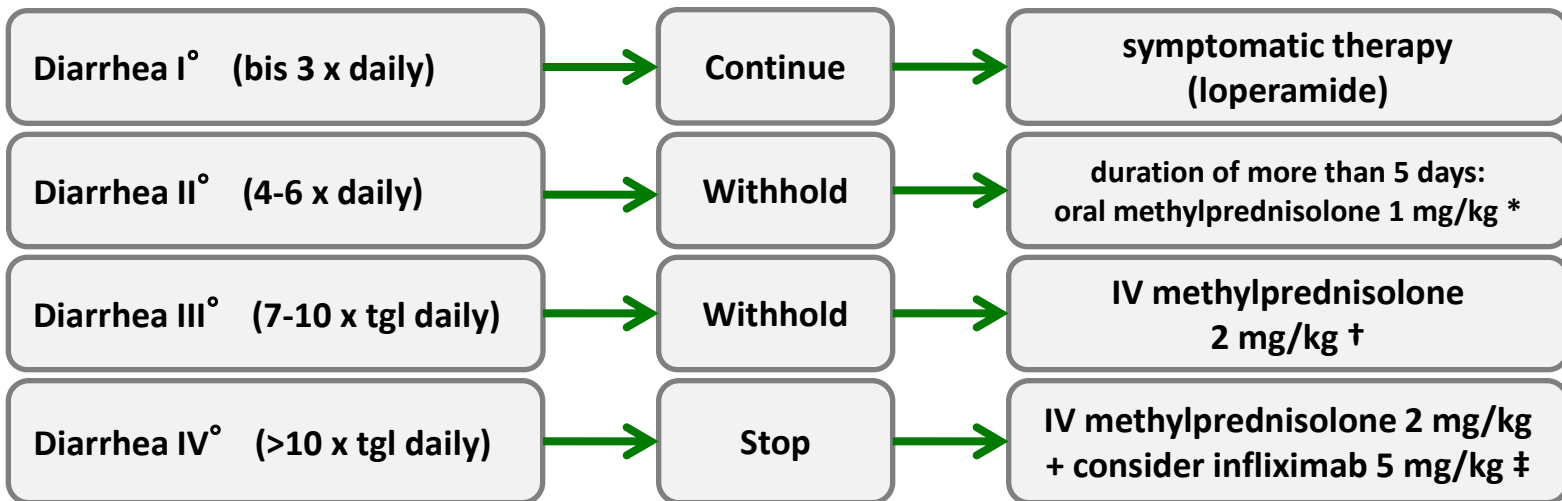


* Prophylactic antibiotic therapy with ciprofloxacin 500 mg bid orally, ulcer prophylaxis with PPI, oral substitution of potassium. Cave: reduced bioavailability of oral steroids, in case of no improvement treat like hepatitis III°

† Diagnostics with ultrasound/ abdominal CT scan, HBV-/ HCV-/ CMV-/ EBV serology, electrophoresis, ANA, ANCA, ASMA, AMA, anti-LKM1, anti-SLA, consider liver biopsy. In case of improvement, reduce methylprednisolone to 1 mg/kg IV (2 weeks) followed by steroid tapering (1 month), start checkpoint inhibitor only at 10 mg/d prednisolone (8 mg/d methylprednisolone)

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

Management of Colitis PD1/PDL1-Inhibitors



* Stool diagnostics (exclude C-diff.). Prophylactic antibiotic therapy with ciprofloxacin 500 mg bid orally, ulcer prophylaxis with PPI, oral substitution of potassium. Cave: reduced bioavailability of oral steroids, in case of no improvement treat like diarrhea III°

† Diagnostic colonoscopy with biopsy, abdominal CT scan in case of left-sided colitis (exclude diverticulitis). In case of improvement, reduce methylprednisolone to 1 mg/kg IV (2 weeks) followed by steroid tapering (1 month), start checkpoint inhibitor only at 10 mg/d prednisolone (8 mg/d methylprednisolone)

‡ pre-therapeutic HBV/ HCV/ CMV/ Tb-(Quantiferon) serology, infliximab contraindicated in case of perforation/ sepsis; application 2h IV via 1,2 µm filter (up to 15% infusion reactions), consider retreatment on day 15

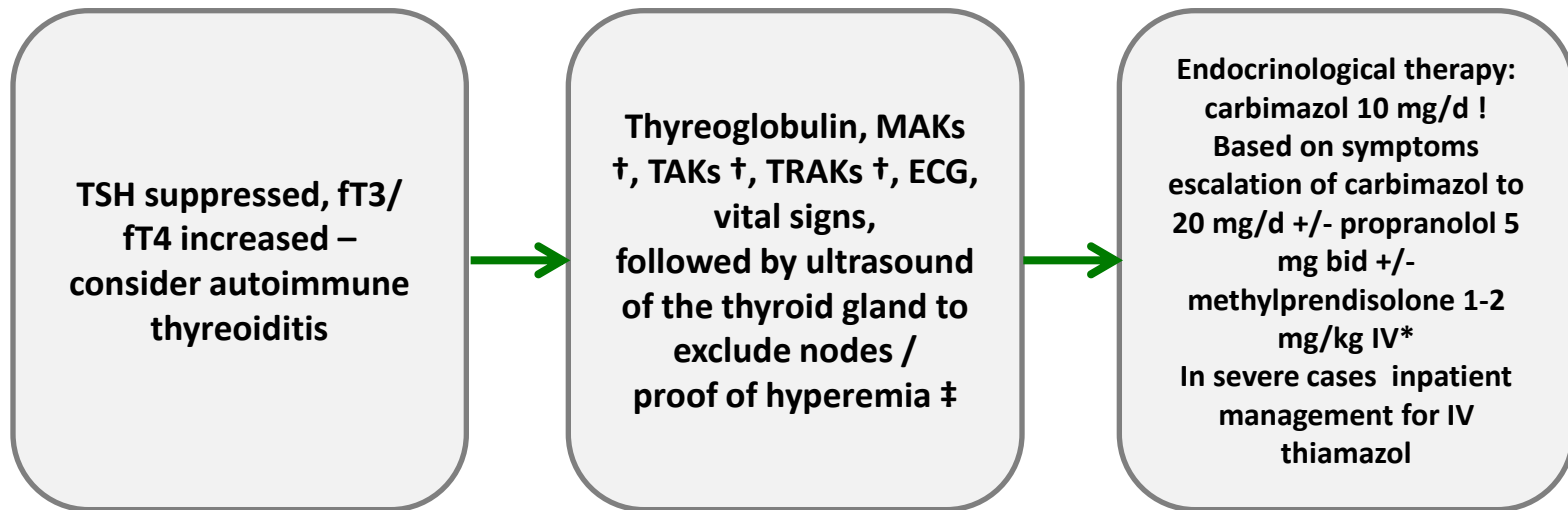
Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

Management of Thyreoiditis

PD1/PDL1-Inhibitors

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- † MAKs: anti-TPO antibody, TAKs: anti-thyreoglobulin antibody, TRAKs: anti-TSH-receptor antibody
- ‡ ultrasound of the thyroid gland
- ! Under carbimazol, withhold treatment with checkpoint inhibitor and start weekly controls of TSH/ fT3/ fT4/ blood count, ALAT/ASAT/AP, continue IO therapy with decreasing fT3/ fT4
- * Prophylactic antibiotic therapy with ciprofloxacin 500 mg bid orally, ulcer prophylaxis with PPI, oral substitution of potassium. Cave: reduced bioavailability of oral steroids,

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

- **Further supportive and palliative issues**
 - **Pain management**
 - **Palliative Care**

Analgesia

(Deutsche Gesellschaft für Schmerztherapie Praxisleitlinie Tumorschmerz 2014

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- **Non-opioids; WHO Step 1**

Diclofenac resinate, ibuprofen and / or metamizole, paracetamol (acetaminophen)

- **Mild opioids; WHO Step 2**

Tramadol (preferentially „retard“-formulations) or tilidine / naloxone (also as „retard“-formulations)

- **Strong opioids; WHO Step 3**

Morphine, buprenorphine (sublingual or transdermal), fentanyl (transdermal), hydromorphone, oxycodone, as a back-up levomethadone. The dose of opioids should be titrated step by step according to the analgetic effect.

- **Additional drugs – „adjuvants“**

Gabapentin, pregabalin, carbamazepine, amitriptyline, bisphosphonates

Palliative Care

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- “...expert consensus that **combined standard oncology care and palliative care** should be **considered early in the course of illness** for **any patient with metastatic cancer and/or high symptom burden**.”¹
- “Palliative care should be **initiated by the primary oncology team** and augmented by **collaboration** with an interdisciplinary team of palliative care experts.”²
- “Expert **palliative care**, including effective control of pain and other symptoms, **should be a priority**.”³

¹ Smith et al, J Clin Oncol 30 880-887, 2012

² Levy et al, J Natl Compr Canc Netw 10:1284-1309, 2012

³ Cardoso et al, Breast 21:242-252, 2012