Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2020.1

Supportive Care and Management of Side Effects

Guidelines Breast
Version 2020.1

Supportive Care and Management of Side Effects

- **Versionen 2002–2019:**
  Albert / Bauerfeind / Brunnert / Bischoff / Costa / Dall / Diel / Fersis / Friedrich / Friedrichs / Gerber / Göhring / Hanf / Harbeck / Heinrich / Huober / Jackisch / Lisboa / Lück / Lüftner / von Minckwitz / Möbus /Müller / Nitz / Oberhoff / Rody / Schaller / Scharl / Schmidt / Schneeweiss / Schütz / Solomayer / Souchon / Stickeler / Thomssen / Untch
- **Version 2020:**
  Müller / Albert

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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

- **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).

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

- **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)**

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Assessment of toxicity

Acute Toxicity (according to WHO[1] or NCI-CTC[2])

Acute toxicities should be asked for and documented after every treatment course **LoE 5 D AGO ++**

Grade		Information required
0	none	organs involved
1	mild	type of toxicity
2	moderate	time interval after treatment
3	severe	effect on general health status
4	life threatening	treatment required
5	death	recovery achieved

Long term toxicity (= secondary diseases after tumour therapy)

Long term surveillance and documentation in regular intervals (acc. ICPC[3] following symptoms or acc. ICD-10-GM[4] following diagnoses) **LoE 5 D AGO ++**

Acute Toxicity (NCI CTCAE vs 5.0, 2017)

- **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.**

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

* MedDRA - Medical Dictionary for Regulatory Activities

Chemotherapy – Acute Toxicities I

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
Alkylating antineoplastic agent												
Cyclophosphamide	4	2	5	5	1	-	1	3	2	3	3	3
Anti-Metabolites												
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
Platinum-complexes												
Cisplatinum	4	2	5	3	2	5	-	4	2	5	4	4
Carboplatin	4	-	5	4	-	-	-	4	4	4	4	-
Anthracyclines / Anthrachinones												
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
Taxanes												
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
Further tubulin-targeting drugs												
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)	HEPATOBILIARY 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	-	Hyponatriaemia
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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- unknown (based on available data incidence not assessable)

Endocrine Therapy – Toxicities

DRUG	INFECTIONS AND INFESTATIONS	NEOPLASMS BEN., MALIGNANT AND UNSPECIFIED (INCL CYSTS & POLYPS)	BLOOD & LYMPH. SYST. DISORDERS	IMMUNE SYSTEM 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
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)	HEPATOBILIARY 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 (≥ 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)

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...“ 2018

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	Oxford		
	LoE	GR	AGO
▪ Avoidance of highly infection-risking behavior or situations	5	D	+
▪ Prophylactic treatment in low-risk patients	1a	B	-
▪ Prophylactic treatment in high-risk* patients (e.g. according to NCCN Guidelines) with			
▪ Antibiotics	1a	A	++
▪ Anti-fungal agents (triazole)	1a	B	+/-
▪ Virostatics in solid tumors	5	D	-
▪ Granulocyte colony-stimulating factors	1a	A	++

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

Hepatitis B virus screening before chemotherapy

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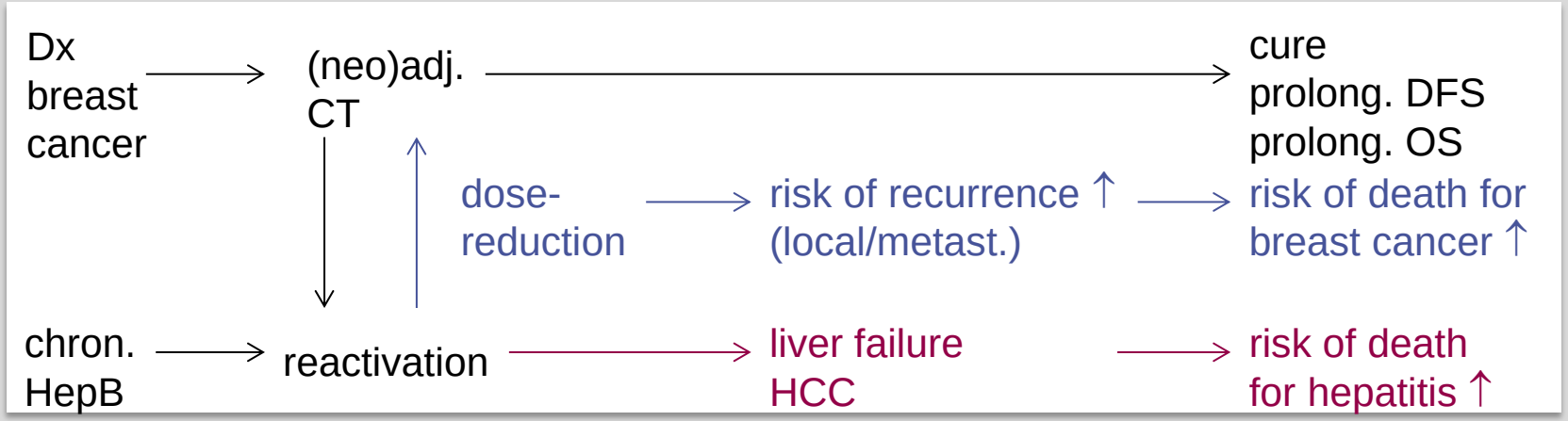
	Oxford LoE	GR	AGO
▪ **Hepatitis B virus screening before adjuvant chemotherapy (HBsAG, anti-HBC)**	2c	B	+
In case of positive serology or reactivation:			
▪ **Interruption of chemotherapy**	5	D	++
▪ **Prophylactic therapy with virustatic drugs if HBV-DNA detected (according AGIHO/DGHO – recommendations)**	1b	A	++
▪ **Hepatitis C virus screening before chemotherapy**	5	D	+/-

Interaction Hepatitis B and Tumour Therapy



„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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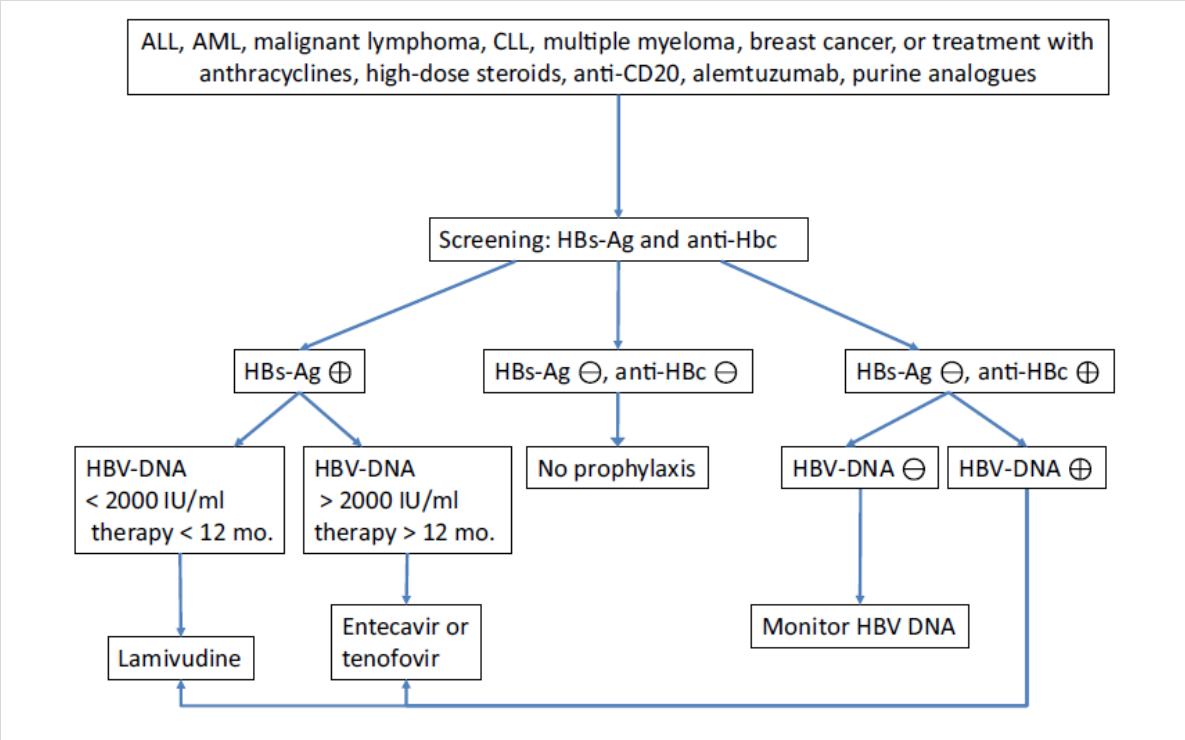

Sandherr M et al. Ann Hematol. 2015 Sep;94(9):1441-50

International recommendations on Hepatitis B virus screening

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

Organization	Recommendation	Tests to Be Done
Centers for Disease Control and Prevention	Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppresssion 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

Di Bisceglie AM et al. *Hepatology.* 2015 Feb;61(2):703-11.

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

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Secondary Malignancies I

	Oxford LoE	Oxford GR
With regard to solid tumors, chemotherapy induced secondary malignancies are rare events		2a
Alkylating agents increase the risk of leukemia dose-dependently to a total of 0.2–0.4 % within 10–15 years		2a
Anthracycline-containing regimens increase the risk of MDS and leukemia to 0.2–1.7 % within 8 to 10 years		2a
PARP-inhibitors are associated with an increased risk of AML and MDS to 0.5–1%		2b
Radiotherapy increases the risk of leukemia by 0.2–0.4% in patients treated with anthracycline-containing chemotherapy		2b
Tamoxifen approximately doubles the risk for developing endometrial cancer (in pts. older than 55y at start of therapy)		2b

Secondary Malignancies II (After Radiotherapy)

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	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**	**1a**
▪ **Enhanced risk especially among ever smokers**	**2b**
▪ **No difference of secondary malignancy between PBI und WBI**	**2c**

Side Effects According Organ Systems
Incidence, Prevention, Therapy

3. *Blood and Lymphatic System Disorders*

- **Anemia**
- **Neutropenia**
- **Febrile Neutropenia (FN)**

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

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	Oxford		
	LoE	GR	AGO
▪ Indicated in asymptomatic anemia	1a	B	-
▪ Therapy and secondary prophylaxis in CT-induced anemia	1a	A	+
▪ Adjuvant setting	1b	A	+
▪ Neoadjuvant/metastatic setting	1a	A	+/-
▪ In dose-dense / dose-escalated CT (iddETC)	1b	A	+
▪ Treatment start at Hb-levels < 10 g/dL	1a	A	+
▪ Target Hb 11–12 g/dL	1a	A	+
▪ Improvement of outcome (DFS, OS)	1a	B	--
▪ Risk of thromboembolic events is increased by use of ESAs	1a	A	

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

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**

J Clin Oncol 2016 (34): 1197-1209

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Practical Use of ESAs

- **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 ß: 30.000 IE weekly s.c.**
  - **Darbepoetin: 2,25 µg/kg s.c. weekly or 500 µg 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**

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Granulocyte Colony-stimulating Factors

	Oxford LoE	Oxford GR	Oxford 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 use 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

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Definition (oral temperature of >38.5° C or two consecutive readings of >38° C for 2 h in a patient with an ANC of <500 cells/mm^3 or expected to fall to <500 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 initially 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

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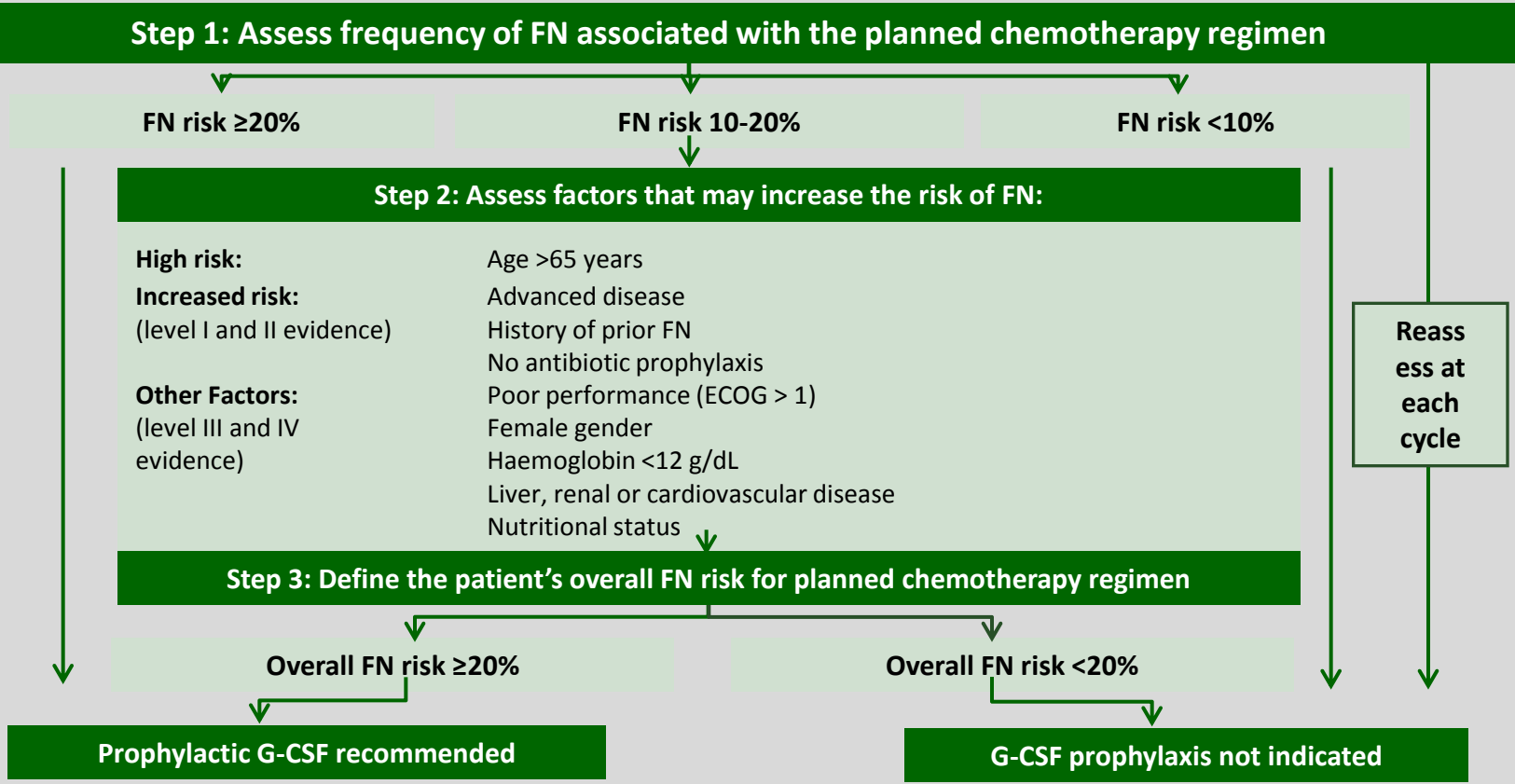

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4. Endocrine disorders

Therapy-associated Amenorrhea (CRA, CIA, TIA)

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	Oxford LoE
▪ CRA may be permanent or temporary (depending on age of the patient and type of chemotherapy)	2b
▪ The risk of CRA increases with patient‘s age and duration of the chemotherapy	2b
▪ CRA is an imperfect surrogate for menopause and fertility	5
▪ Adjuvant endocrine therapy with GnRHa induces reversible amenorrhea, but delays conception to a less fertile period	5
▪ Ovarian reserve of women who remain premenopausal after CTX is reduced	2b
▪ CRA is associated with improved outcome (DFS/OS)	1b

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

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5. Psychiatric Disorders

- Depression
- Fatigue
- Cognitive impairment
- Sleep disturbances

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(Therapy-Associated) Depression

	Oxford LoE	Oxford GR	AGO
▪ Depression is an often reported adverse event in breast cancer patients (20–30%)	2a	B	
▪ Psychological interventions are effective to improve mood, but not survival in distressed and depressed patients	1b	A	
▪ Antidepressents have shown to improve depression in breast cancer patients	1b	A	
▪ Regular exercise participation can prevent depression in breast cancer survivors	2b	B	+

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(Therapy-Related) Fatigue

	Oxford LoE	GR	AGO
▪ Fatigue frequent in breast cancer patients (30–60%)	2a	B	
▪ Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue	1a	A	++
▪ Psycho-social interventions specifically addressing fatigue efficient in reducing fatigue	1a	A	++
▪ Physical exercise can improve fatigue	1b	D	+
▪ Diet, Yoga can improve fatigue	2b	B	+
▪ Methylphenidate can improve fatigue	1a	D	+

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(Therapy-Associated) Cognitive Impairment

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

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(Therapy-Associated) Sleep Disturbances

	Oxford LoE	Oxford GR	AGO
▪ Sleep disturbances are a common problem in breast cancer patients during and after therapy (20–70%)	2a	B	
▪ Behavioral therapies demonstrated efficacy in treatment of insomnia and improved quality of life	1b	A	++

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6. Nervous system disorders

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

Chemotherapy-Induced Peripheral Neuropathy (CIPN)

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- **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**

<u>Unclear</u>:

- **Other genetic factors (SNPs, mutations)**

Chemotherapy-induced Peripheral Neuropathy – Prevention –

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	Oxford LoE	Oxford GR	AGO
Non drug-based prevention			
▪ Functional training (physical fitness, sensomotoric stimulation training etc.)	5	D	+
▪ Compression treatment (tight surgical gloves, compression stockings)	2b	B	+
▪ Cooling gloves and stockings	2b[a]	B	+/-
▪ Elektro-acupuncture	1b	B	-
Drug-based prevention			
▪ Venlafaxine	2a	C	+/-
▪ Palmitoylethanolamine (PEA) topically or PO	5	D	+/-
▪ A-lipoic-acid (thioctic acid), amifostine, amitriptyline, acetyl-L-car-nitine, carbamazepine, electrolyte solutions, glutathione, Goshajinkigan (GJG), oxcarbazepine, vitamine B, vitamine E, or other compounds[1]	1b	A	-

[1] For list of not recommended drugs, see Hershman et al. 2014

Chemotherapy-induced Peripheral Neuropathy – Therapy –

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	Oxford LoE	GR	AGO
Non drug-based therapy			
▪ Functional training (physical fitness, sensomotoric stimulation training etc.)	2a	C	+
▪ Physiotherapy / physical treatment	5	D	+
▪ acupuncture	2b	B	+
Drug-based therapy			
▪ Menthol locally (1%), capsaicin/lidocain locally	5	D	+
▪ Baclofen/amitryptiline/ketamin-gel	2b	B	+
▪ Duloxetine for therapy of CIPN-induced pain	1b	B	+
▪ Opioids for therapy of CIPN-induced pain	5	D	+
▪ Palmitoylethanolamine (PEA) topically or PO.	5	D	+/-
▪ Venlafaxine	5	D	+/-
▪ Gabapentin, pregabaline	1b	B	+/-
▪ Amitryptiline/ nortripyline, imipramine/desipramine	1b	B	+/-
▪ Acetyl-L-carnitine, lamotrigine, or other compounds[1]	1b	B	-

[1] For list of not recommended drugs, see 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/m² 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 toxicicty	2b	B	+/-
▪ Betablocker-prohylaxis during anthracycline therapy	2a	B	+/-

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Adjuvant Trastuzumab
Cardiac Monitoring for CHF

Oxford LoE: 5 GR: D AGO: ++

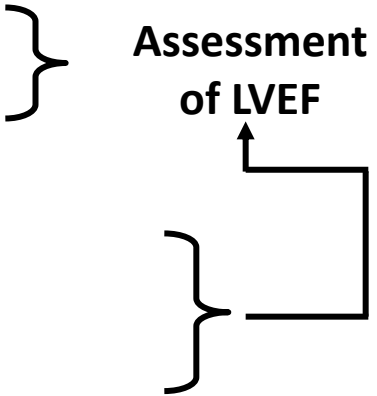
Before start of trastuzumab

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

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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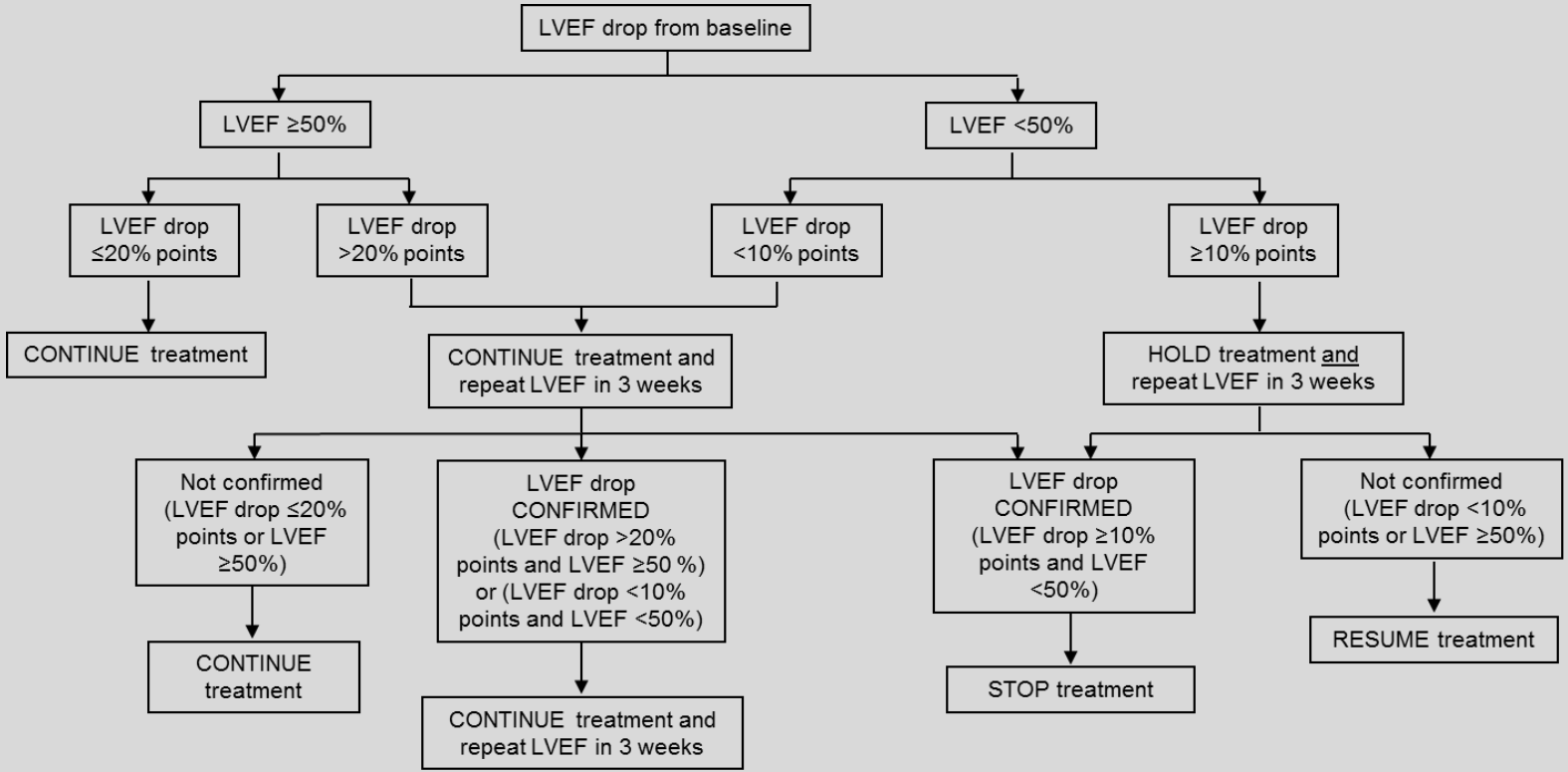
	Oxford LoE	Oxford GR	AGO
Regarding cardiac toxicity			
▪ Trastuzumab simultaneous to radiotherapy	2b	B	+
▪ Trastuzumab simultaneous to epirubicin	2b	B	+/-
▪ Trastuzumab simultaneous to doxorubicin	2b	B	-
▪ Anthracycline simultaneous to radiotherapy	2c	C	-
Regarding lung and breast fibrosis			
▪ Tamoxifen simultaneous to radiotherapy	3	C	+/-
▪ Chemotherapy simultaneous to radiotherapy	1b	B	-

Side Effects of Trastuzumab/Pertuzumab: Algorithm in Case of Cardiac Toxicity



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www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Side Effects According Organ Systems
Incidence, Prevention, Therapy

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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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	Oxford		
	LoE	GR	AGO
▪ After assessment of emetic potential of chemotherapy protocol	5	D	++
▪ Neurokinin-1-receptor-antagonists	1b	A	++
▪ Dexamethasone	1a	A	++
▪ 5-HT_3-antagonists	1b	A	++
▪ Fixed antiemetic combination therapy	1b	A	++
▪ Rescue Medication			
• Olanzapine	1b	A	+
▪ Levomepromazine, benzodiazepines ▪ Cannabinoids, ginger	3b	C	+

Antiemetic Therapy
https://www.mascc.org/antiemetic-guidelines

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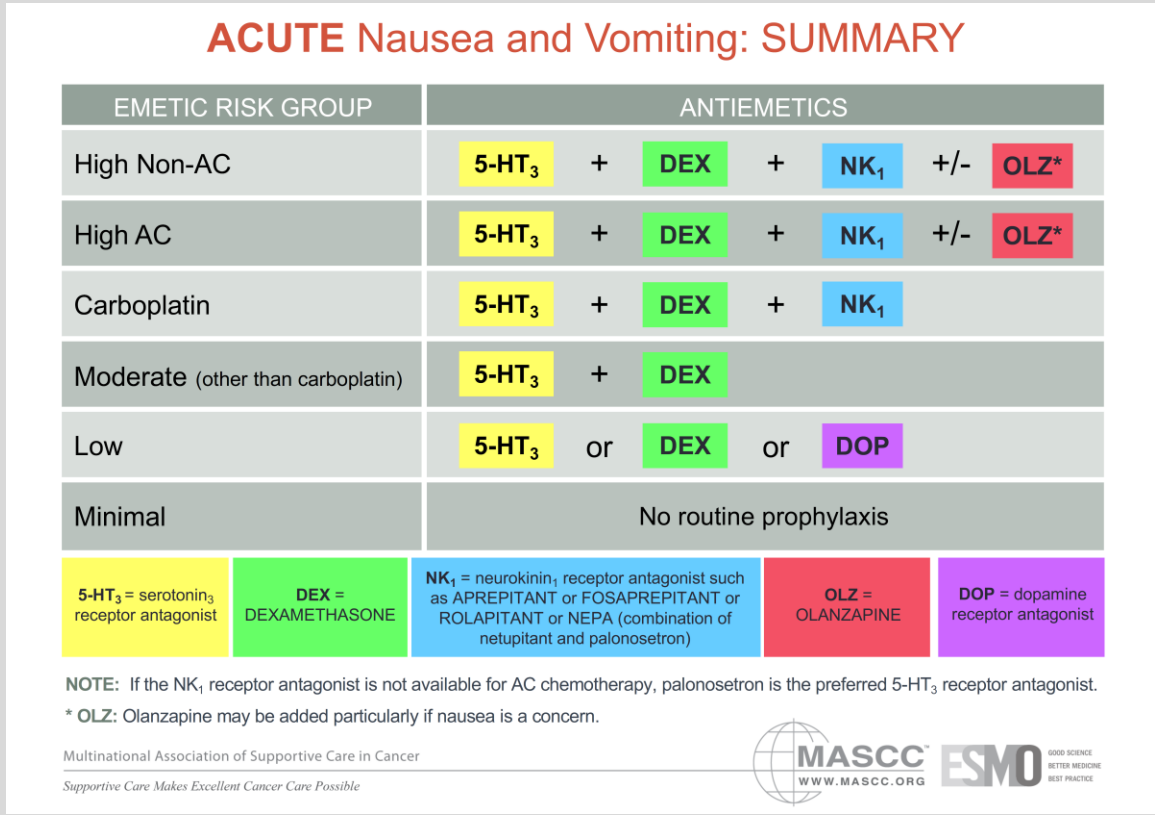

Antiemetic Therapy
https://www.mascc.org/antiemetic-guidelines

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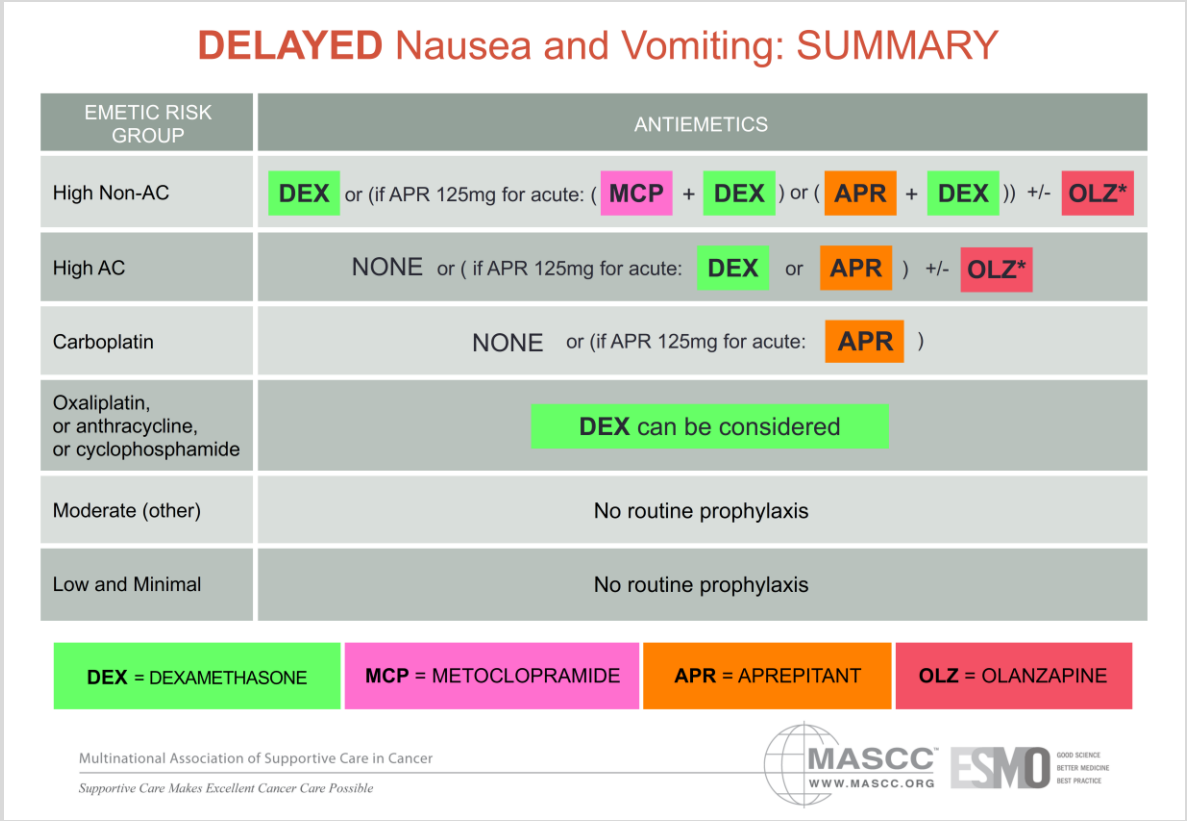

Supportive Therapy
Antiemetics

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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
Oxazapine	Olanzepin	10mg/d for d1-4 Ggf. 5mg/d for d1-4	Sedation, weight gain	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
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
▪ **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 brushs**
   - **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/combinationes

Prevention of Everolimus-Induced Stomatitis Using Dexamethasone Mouthwash

- **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 15 mg per 5 mL oral solution (swish for 2 min and spit) for at least 8–12 weeks***
- **Results: after 13 wks exposition all-grade incidence of stomatitis 27% (BOLERO 67%), ≥ grade 2 events 9% (BOLERO 27%)**

* **Alternatively Hydrocortison: Hydrocortisonacetat-Suspension 0,5 % with Lidocainhydrochlorid and Dexpanthenol (Germany: Arzneibuchrezeptur NRF 7.14.)**

Rugo et al., Lancet Oncol 2017, , Jones et al. Oncologist 2019

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Guidelines Breast
Version 2020.1

Mucositis

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

- **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

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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***

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Constipation

Important Side Effect of Opioid Treatment

- **Bulging agents**
  - **Psylium, 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**

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9. Skin & Subcutaneous Tissue Disorders (Alopecia)

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Skin toxicities

	Oxford		
	LoE	GR	AGO
▪ Avoidance of chemotherapy-induced alopecia by cooling the patient‘s scalp*	1b		+/-
▪ Prophylaxis of hand-foot-syndrome using urea containing lotions (5-10%)	1b		+
▪ Prophylaxis of nail changes and hand-foot-syndrome by cooling hands during application of docetaxel	2b		+

* Substance- and regimen specific

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

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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 $p < 0.001$

Two Metaanalyses: 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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	Oxford		
	LoE	GR	AGO
▪ Dexrazoxane for treatment of anthracycline-extravasations (exception: liposomal Anthracyclines)	2b	B	++
▪ Hyaluronic acid for treatment of taxane/ vinorelbine-extravasations	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**
- **PI3-Kinase-Inhibitoren (Alpelisib)**

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

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	Oxford LoE	Oxford GR	AGO
Trastuzumab			
▪ Cardiotoxicity in the adjuvant setting (1.0–2.0%)	1b	A	
▪ Troponin I may identify patients at risk for cardiotoxicity	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	
Trastuzumab-Deruxtecan			
▪ Interstitelle Lungenerkrankung, Neutropenie, Übelkeit	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			

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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 an elevated risk of life-threatening arrhythmia *"torsades de pointes"* (TdP)**

Toxicities of new compounds: mTOR-Inhibitor – Everolimus –

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

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Toxicities of new compounds: PARP-Inhibitors – Olaparib, Talazoparib –

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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

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

Primary Prophylaxis with loperamide

LoE		AGO
2b	B	++

Toxicities of new compounds: PIK3CA - alpelisib

Alpelisib+Fulvestrant

UE, %	All Grade	Grad >/=3
Hypergycemia	63,7%	32,7%
Diarrhea	57,7%	6,7%
Nausea	44,7%	2,5%
Decreased appetite	35,6%	< 1% SAE
Rush	35,5%	9,9%
Vomiting	27,1%	< 1% SAE
Weight loss	26,8%	3,9%
Stomatitis	24,6%	2,5%
Fatique	24,3%	3,5
Asthenia	20,4%	1,8
Alopecia	19,7%	0
Mucositis	18,3%	2,1

Regard recommendations for management of side effects (Diabetes mellitus, hyperglycemia, Insulin resistance und metabolic syndrom)

LoE	AGO
2b	B ++

Andre F, et al N Engl J Med 2019;380:1929-1940

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Version 2020.1

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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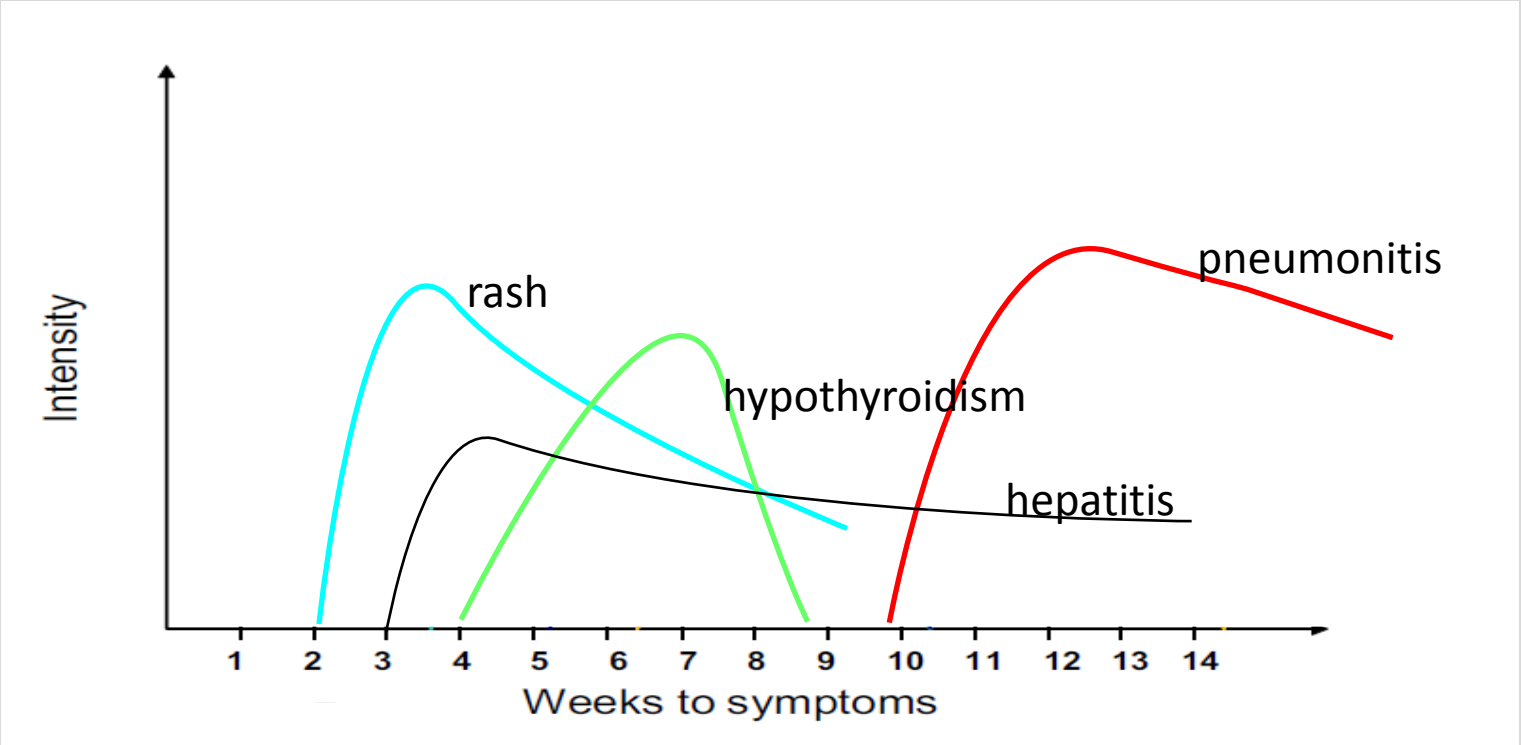

Haanen J et al. Ann Oncol 2017; 28 (suppl 4): 119-142

Immune Checkpoint Inhibitors
– side effects –

- **Adverse events ≥ 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**

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Immune Checkpoint Inhibitors
Toxicities (Total in %)

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	atezolizumab	nivolumab	pembrolizumab
diarrhea	18.6%	13%	18%
colitis	1.1%	2%	1%
exanthema	18.6%	15%	<1%
hepatoxicity	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%

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

Immune Checkpoint Inhibitors
Principles of Adverse Event Management

CTC AE-Grade	Management
1	▪ supportive therapy ▪ close examination ▪ exclusion of infective complications ▪ patient information
2	Like grade 1 but ▪ intermission of therapy until recovery of all irAE to grades 0-1 ▪ consider corticosteroids
3	▪ supportive therapy ▪ IV steroids (e.g. 1-2 mg/kg prednisolone) In case of no improvement within 48 h: ▪ 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

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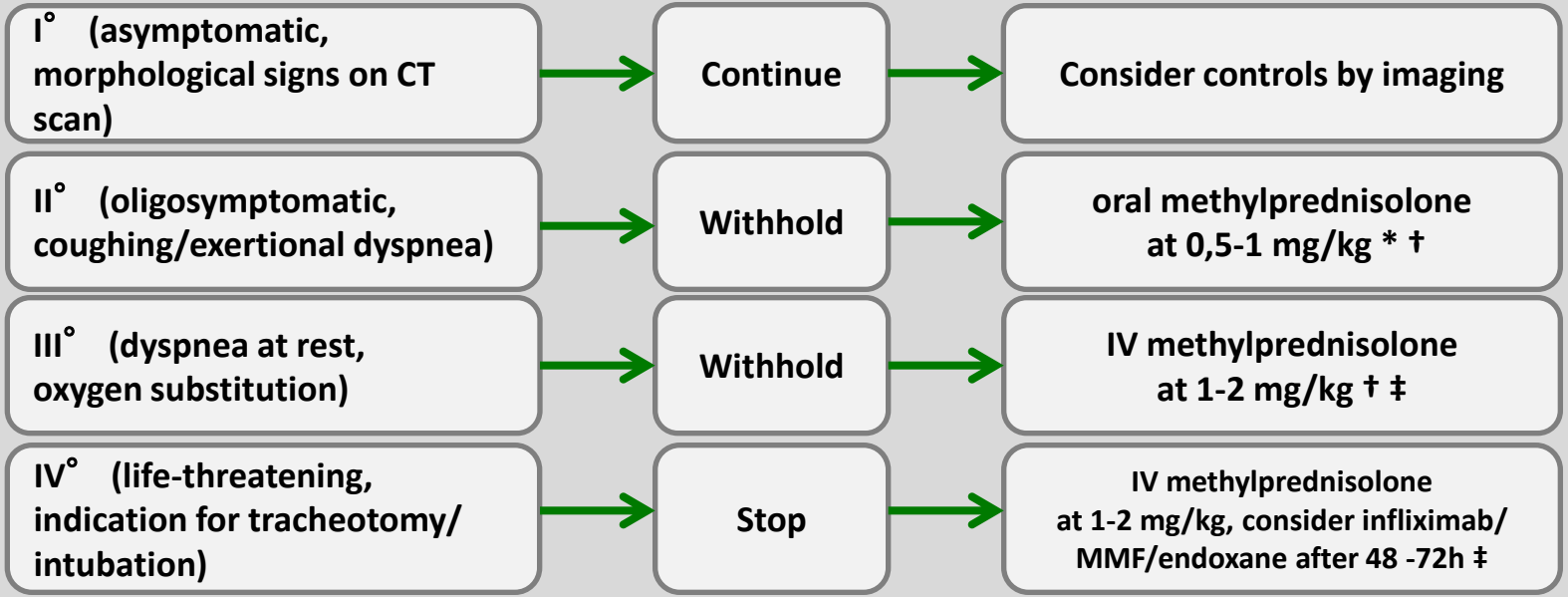
Management of Pneumonitis
PD1/ PDL1 Inhibitors



* 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

‡ > pneumonitits III° bronchoscopy plus lavage / consider biopsy

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

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Management of Nephritis PD1/PDL1-Inhibitors

Guidelines Breast
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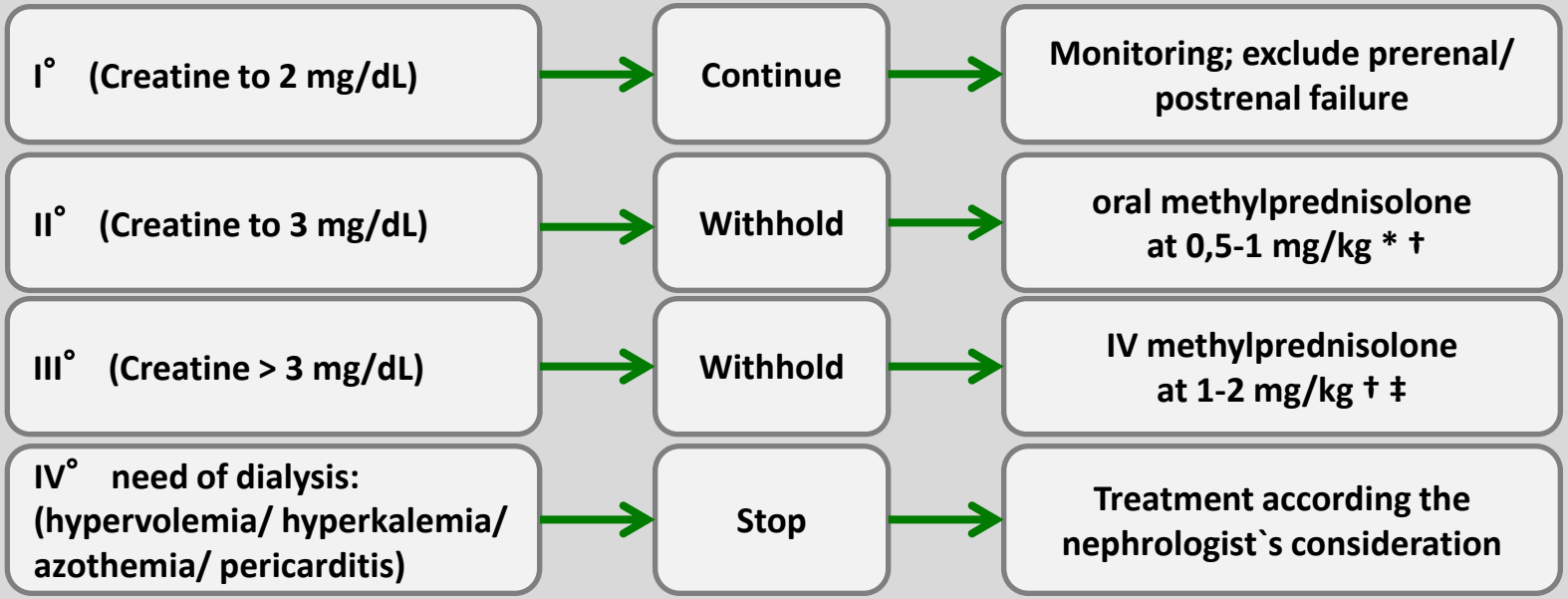

* Prophylactic antibiotic therapy with ciprofloxacin 500 mg bid orally, ulcus prophylaxis with PPI, oral substitution of potassium. In case of no improvement treat like for nephritis III°

† 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

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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: adrenocorticotropic 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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I° (ALAT/ASAT< 3 x ULN and/or total bilirubin < 1,5 x ULN)	Continue	Serum controls before each treatment
II° (ALAT/ASAT < 5 x ULN and/or total bilirubin < 3 x ULN)	Withhold	persisting longer than 5 days: oral methylprednisolone 1 mg/kg * †
III° (ALAT/ASAT > 5 x ULN and/or total bilirubin > 3 x ULN)	Withhold	IV methylprednisolone 2 mg/kg †
IV° (ALAT/ASAT > 20 x ULN and/or total bilirubin > 10 x ULN)	Stop	IV methylprednisolone 2 mg/kg, consider add-on MMF 1000 mg bid after 48h

* Prophylactic antibiotic therapy with ciprofloxacin 500 mg bid orally, ulcus 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

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Diarrhea I° (bis 3 x daily)	Continue	symptomatic therapy (loperamide)
Diarrhea II° (4-6 x daily)	Withhold	duration of more than 5 days: oral methylprednisolone 1 mg/kg *
Diarrhea III° (7-10 x tgl daily)	Withhold	IV methylprednisolone 2 mg/kg †
Diarrhea IV° (>10 x tgl daily)	Stop	IV methylprednisolone 2 mg/kg + consider infliximab 5 mg/kg ‡

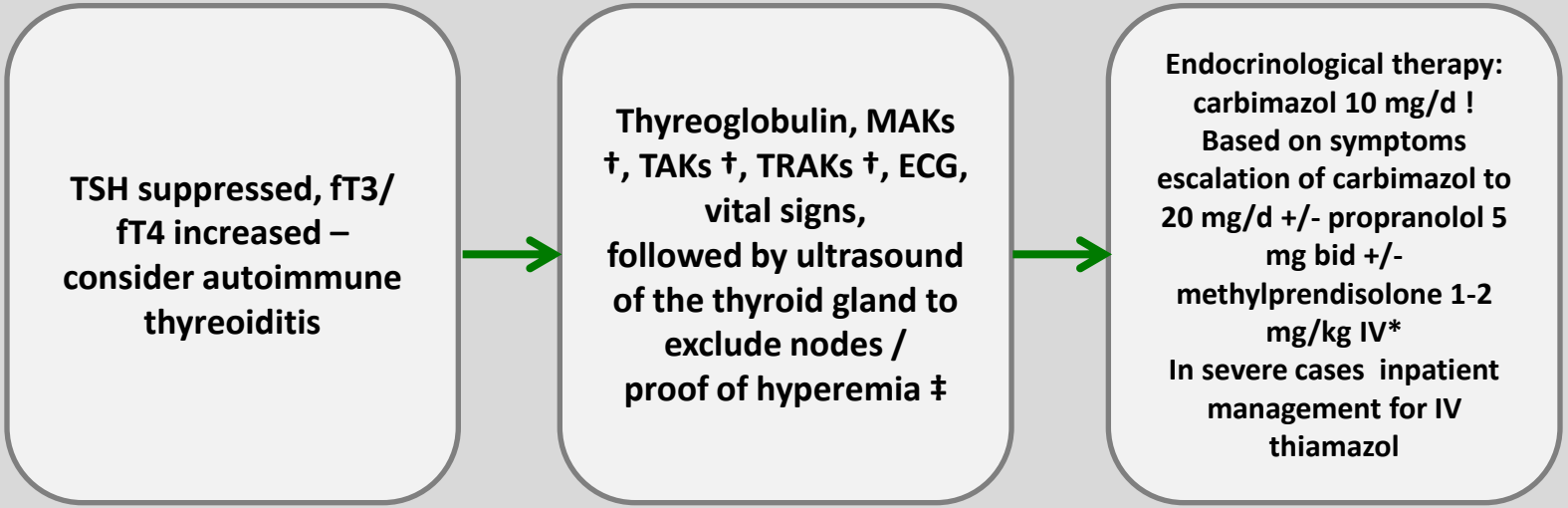
* Stool diagnostics (exclude C-diff.). Prophylactic antibiotic therapy with ciprofloxacin 500 mg bid orally, ulcus prophylaxis with PPI, oral substitution of potassium. Cave: reduced bioavailability of oral steroids, in case of no improvement treat like diarrhea III°

† Diagnostic colonoscopy with biopsy, abdomincal CT scan in case of left-sided colitis (exclude diverticulitis). In case of improvement, reduce methlyprednisolone 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



† 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, ulcus prophylaxis with PPI, oral substitution of potassium. Cave: reduced bioavailability of oral steroids,

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

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

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Nutrition deficiency

- **Nutrient deficiency is a common medical problem affecting 15-40% of cancer patients. It impairs their quality of life and can affect the success of treatment.**
- **Integration of nutritional advice into clinical management recommended**
- **For nutrition see S3 guideline Palliative care and supportive therapy**

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Analgesia

- **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“**
  Canabinoide, Gabapentin, pregabalin, carbamazepine, amitriptyline, bisphosphonates

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Palliative Care

- **All patients should be offered palliative care after the diagnosis of a non-curable cancer, regardless of whether a tumour-specific therapy is carried out.**
- **Specialized palliative care should be integrated into oncological decision-making processes, e.g. by participating in interdisciplinary tumor conferences.**
- **Patients with incurable cancer who are cared for in structures of specialized palliative care (palliative care ward, specialized outpatient care such as SAPV) should have access to oncological councelling.**

https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/