Guidelines Breast
Version 2021.1E

Supportive Care and Management of Side Effects

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Version 2021.1E

Supportive Care and Management of Side Effects

- **Versionen 2002–2020:**
  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 2021:**
  Mundhenke/Nitz

- **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 1.3 –Februar 2020 AWMF-Registernummer: 032/054OL**

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

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 ++**

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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.**

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

* **MedDRA - Medical Dictionary for Regulatory Activities**

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
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 frequent (≥ 1/10). - unknown (based on available data incidence not assessable)

Chemotherapy – Acute Toxicities II

	SYSTEM ORGAN CLASS										
DRUG	RESPIRAT., HORAC. & MEDIA-STINAL DIS.	GASTROINT.DISORD. (NAUSEA, EMESIS)	HEPATOBILIARY DISORDERS	SKIN & SUBCUT. TIS. DISORD. (ALOPECIA)	MUSCULOSKELETAL & 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)	MUSCULOSKEL ETAL & CONNECTIVE TISSUE DISORDERS	RENAL& URINARY DISORDERS	PREGN., PUERPER. & PERINAT. COND.	REPRODUCT. SYS. & BREAST DISORDERS	GENERAL DIS. & ADMINISTRATIO N 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:

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- unknown (based on available data incidence not assessable)

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

	Oxford LoE	Oxford GR
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		
▪ Interstitial lung disease (ILD), neutropenia, nausea	2b	B

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%

	LoE	GR	AGO
Primary Prophylaxis with loperamide	2b	B	++

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

Common Toxicities with antiHER2-TKI: Tucatinib, Trastuzumab + Capecitabine

Event	Capecitabine+Tucatinib+Trastuzumab	
	Any grade (%)	≥3 grade (%)
Any adverse event	99.3	55.2
Diarrhea	80.9	12.9
PPE syndrome	63.4	13.1
Nausea	58.4	3.7
Fatigue	45.0	4.7
Vomiting	35.9	3.0
Stomatitis	25.5	2.5
Reduced appetite	24.8	0.5
Headache	21.5	0.5

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

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	Supportive Care and Management of Side Effects		

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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 –

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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: 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

Consider recommendations for management of side effects (diabetes mellitus, hyperglycemia, insulin resistance and metabolic syndrome)

LoE	GR	AGO
2b	B	++

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

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
Cough	22,7	0,7
Pleural effusion	2,1	1,7
PPE	1,4	0,3

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Immune Checkpoint Inhibitors

- **Therapeutic approaches (antibodies)**
  - **PD1 /PD-L1**

    PD1
    - **nivolumab**
    - **pembrolizumab**

    PD-L1
    - **atezolizumab**
    - **durvalumab**
    - **avelumab**

Immune Checkpoint Inhibitors
Time Course of Adverse Events, ex. Nivolumab

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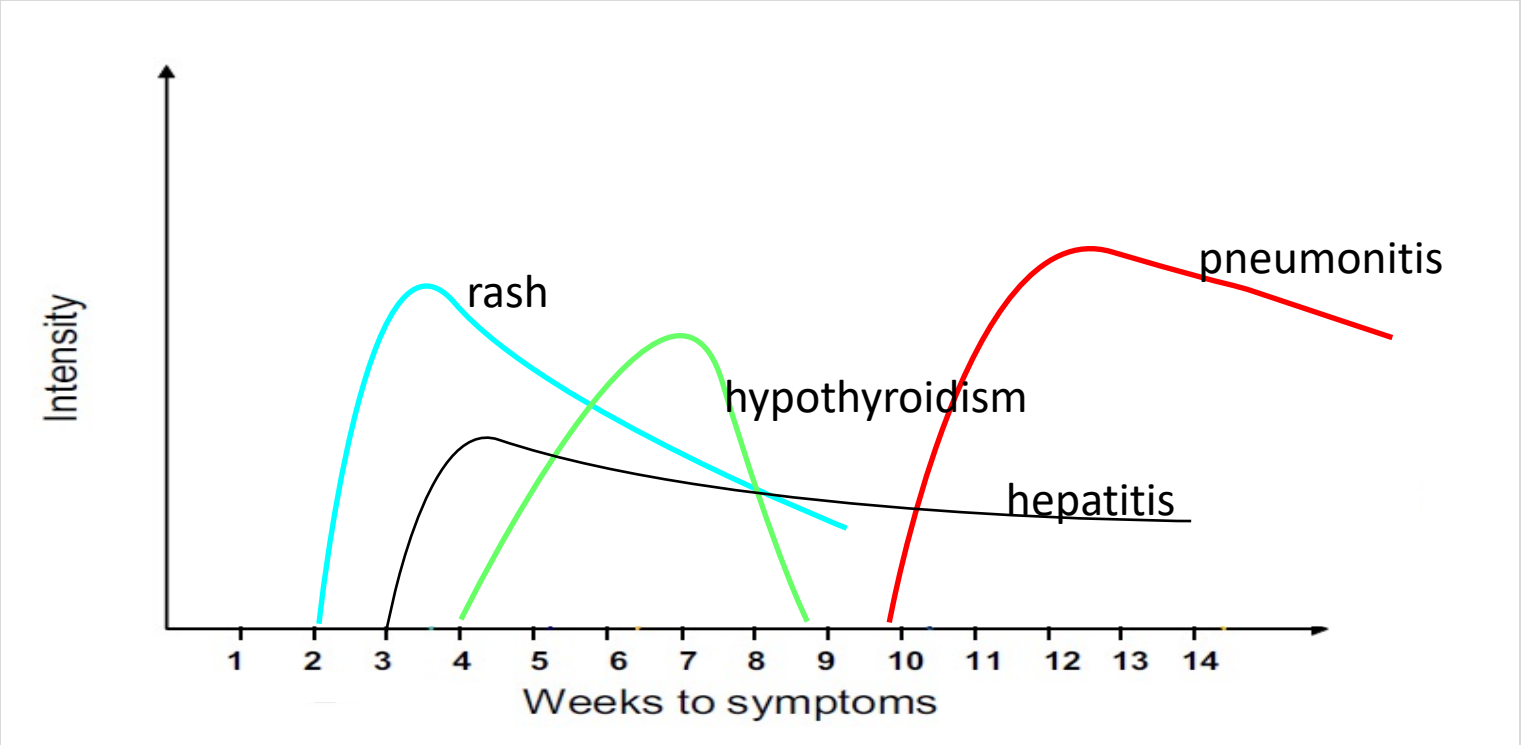

Haanen J et al. Ann Oncol 2017; 28 (suppl 4): 119-142

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

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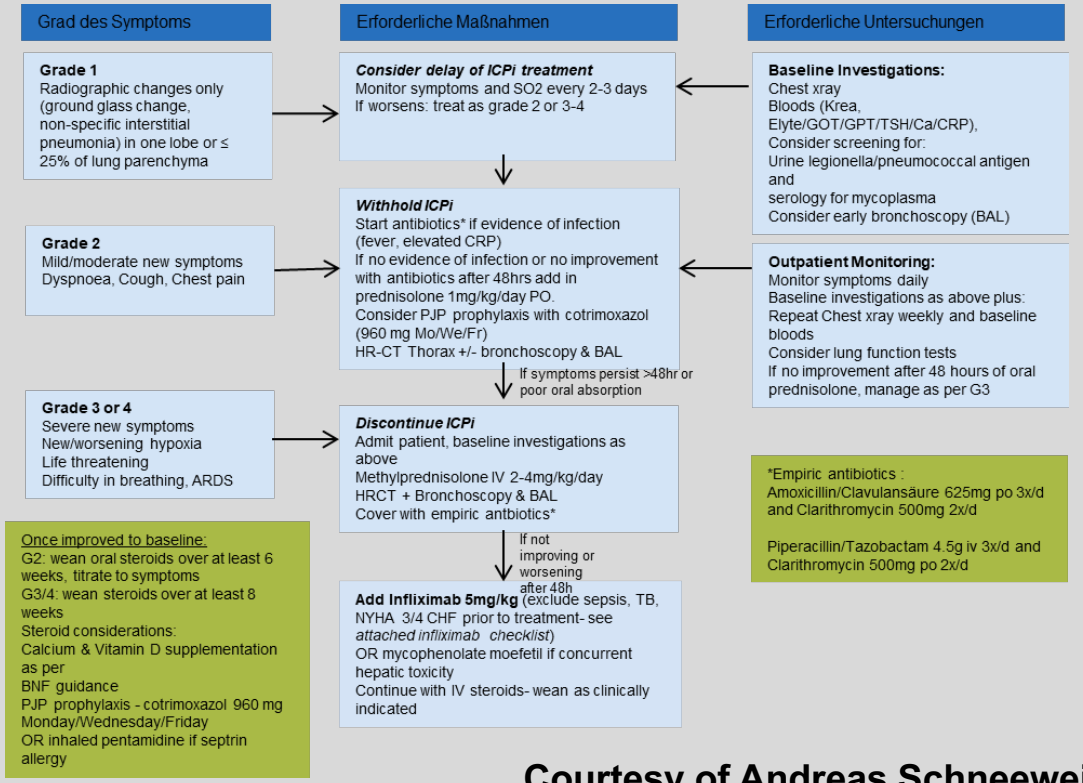
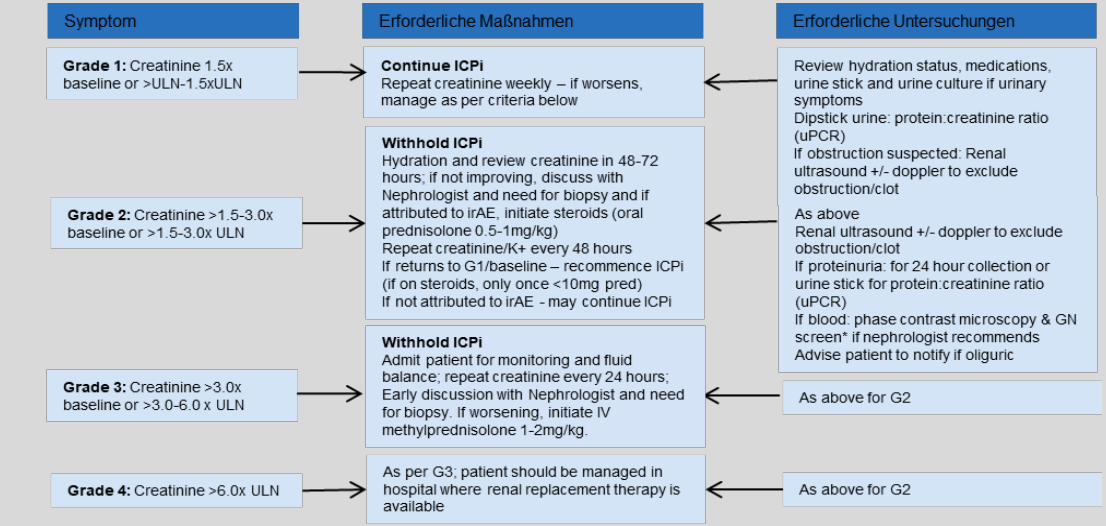
CTC AE-Grade	Management
1	▪ supportive therapy ▪ close examination ▪ exclusion of infective complications ▪ patient information
2	Like grade 1 but ▪ intermission of therapy until recovery of all irAE to grades 0-1 ▪ consider corticosteroids
3	▪ supportive therapy ▪ IV steroids (e.g. 1-2 mg/kg prednisolone) 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

Pneumonitis



Courtesy of Andreas Schneeweiss, NCI

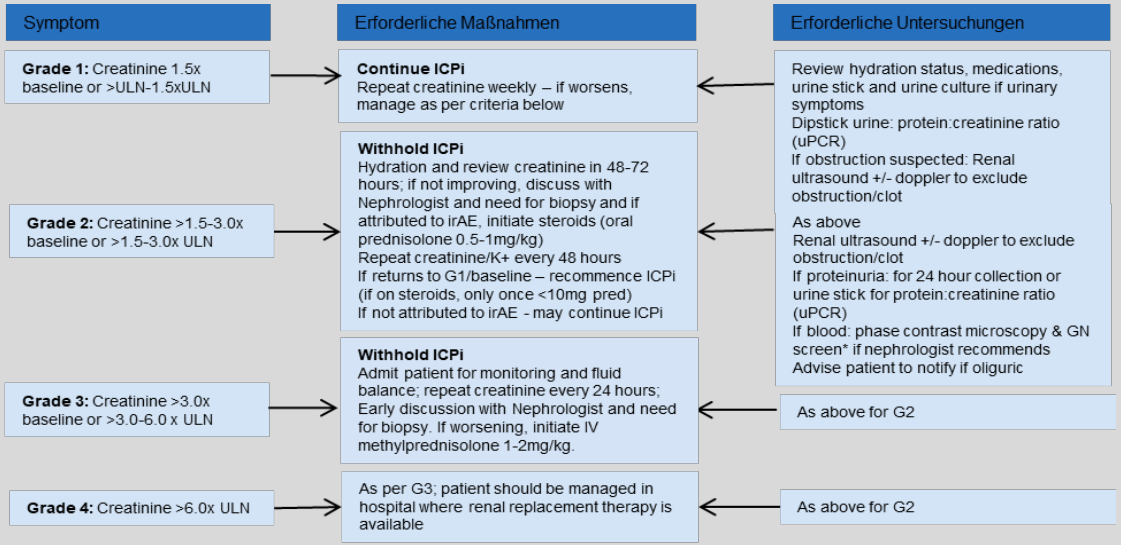
Nephrotoxizität



Renal injury occurs in around 1-4% of patients treated with ICPi's, usually in a pattern of acute tubulo-interstitial nephritis with a lymphocytic infiltrate (Cortazar et al 2016 Kid Int)
Attention needs to be paid to the *patient's baseline creatinine* & not just abnormal results per biochemistry ULN
Confounding diagnoses include dehydration, recent IV contrast, urinary tract infection, medications, hypotension or hypertension
Early consideration for renal biopsy is helpful which may negate the need for steroids and determine if renal deterioration related to ICPi or other pathology
Oliguria should prompt inpatient admission for careful fluid balance and plan for access to renal replacement therapy
Steroid wean: begin to wean once creatinine G1; G2 severity episode– wean steroids over 2-4 weeks; G3/4 episode- wean over ≥4 weeks
If on steroids for >4 weeks – PJP prophylaxis, calcium/Vitamin D supplementation, gastric protection and check afternoon glucose for hyperglycemia
*Glomerulonephritis screen: ANA, Complement C3,C4, ANCA, anti-GBM, Hepatitis B and C, HIV, Immunoglobulins and protein electrophoresis

Courtesy of Andreas Schneeweiss, NCI

Hypophysitis



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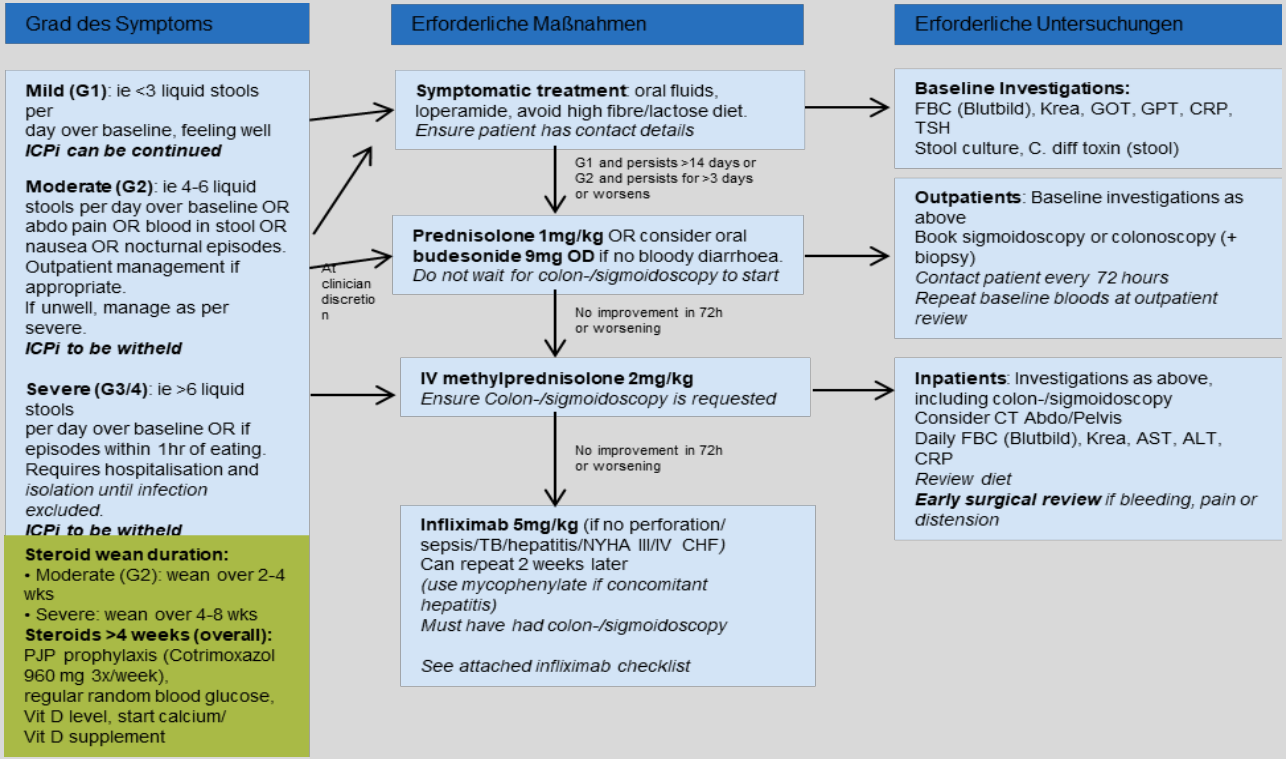
Courtesy of Andreas Schneeweiss, NCI

Diarrhoe und Kolitis



Courtesy of Andreas Schneeweiss, NCI

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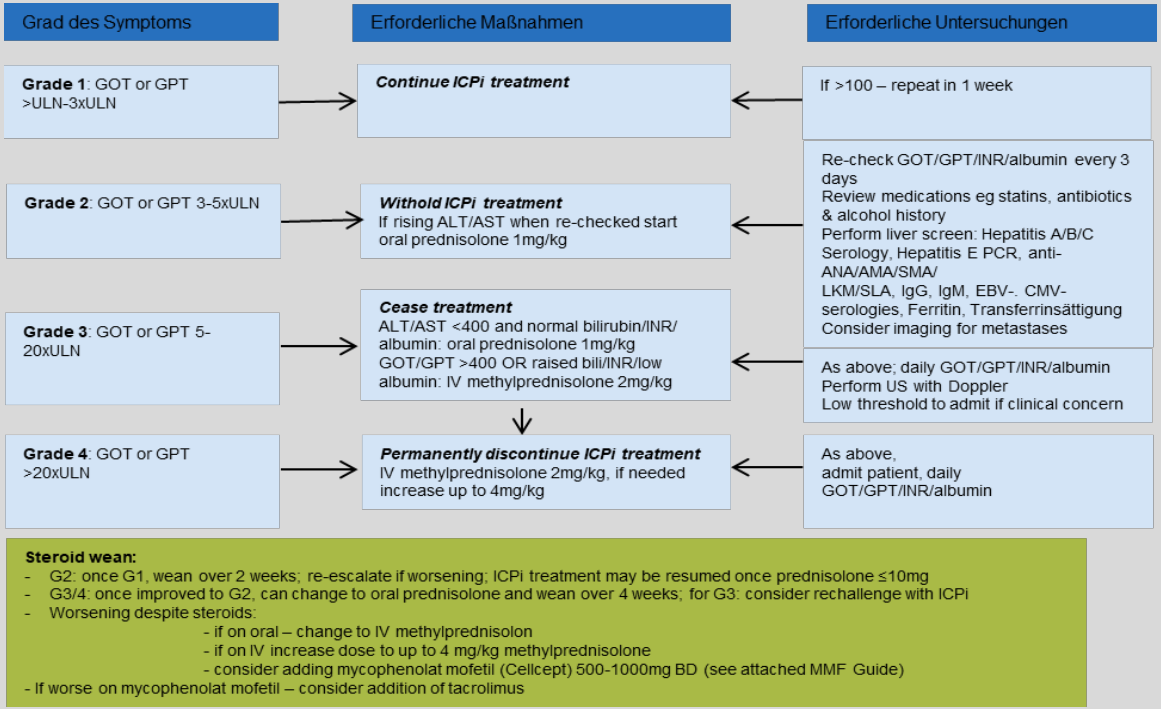
www.ago-online.de

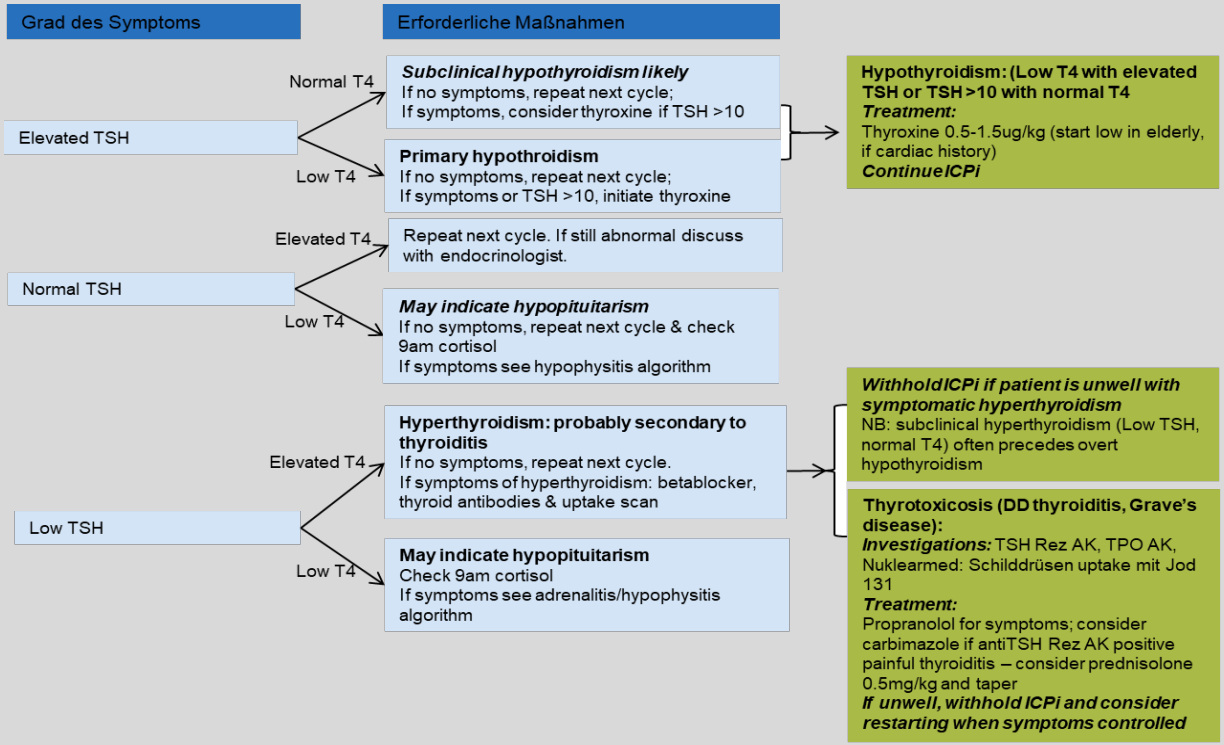
FORSCHEN
LEHREN
HEILEN

Hepatitis



Courtesy of Andreas Schneeweiss, NCI

Thyreoditis



Courtesy of Andreas Schneeweiss, NCI

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Side effects according Organ Systems
Incidence, Prevention, Therapy

1. Infections

- General prophylaxis for infections
- Hepatitis B virus screening
- Covid-19 (see joint guidelines with DGHO)

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

ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2018

	Oxford		
	LoE	GR	AGO
▪ Avoidance of behavior or situations that are associated with high risk for infections	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	+
<u>In case of positive serology or reactivation:</u>			
▪ 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	+/-

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

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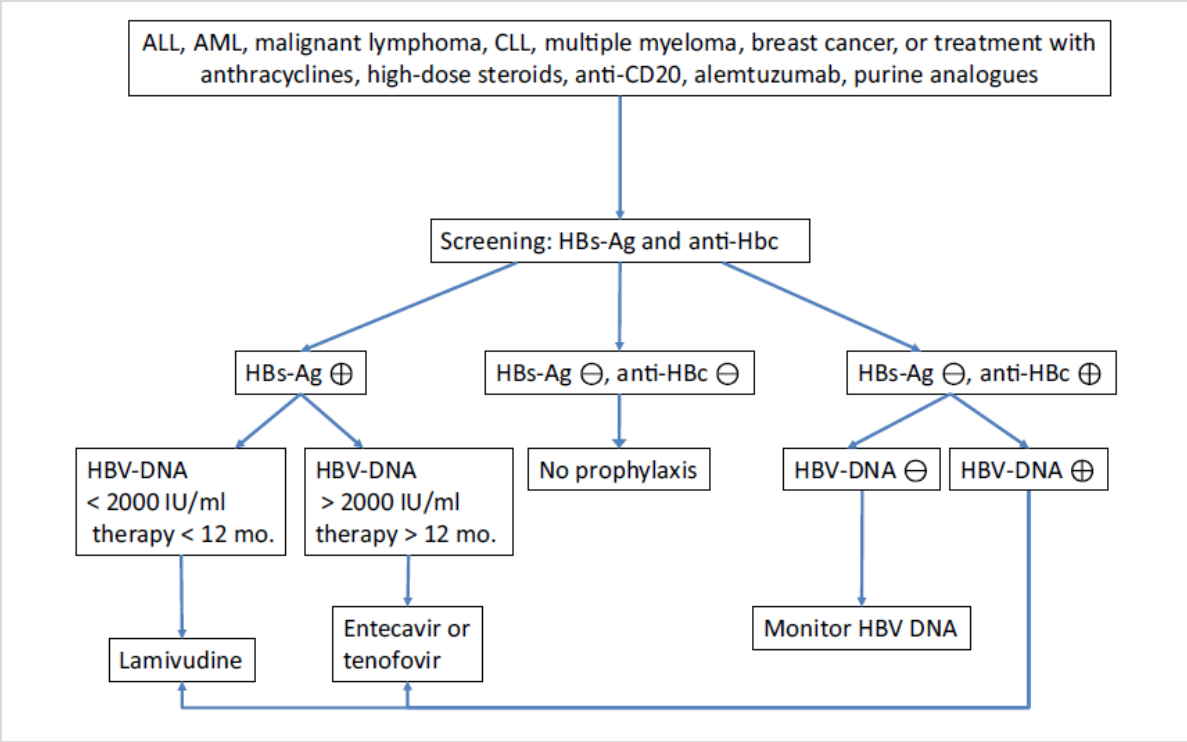

Sandherr M et al. Ann Hematol. 2015 Sep;94(9):1441-50

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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**

Guidelines Breast
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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 CTx-induced anemia	1a	A	+
▪ Adjuvant setting	1b	A	+
▪ Neoadjuvant/metastatic setting	1a	A	+/-
▪ In dose-dense / dose-escalated CTx (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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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**

Granulocyte Colony-stimulating Factors

	Oxford LoE	Oxford GR	AGO
▪ **Primary prophylaxis for expected febrile neutropenia (FN)**			
▪ If expected risk for FN 10–20%	1b	B	+/-
▪ In case of individual risk factors	3b	C	+
▪ If expected risk for FN >20% (e.g. DAC, dose-dense CT)	1a	A	++
▪ **Secondary prophylaxis during chemotherapy (previous FN or neutropenia grade IV > 7 days)**	1b	A	++
▪ **Therapeutic use for FN**	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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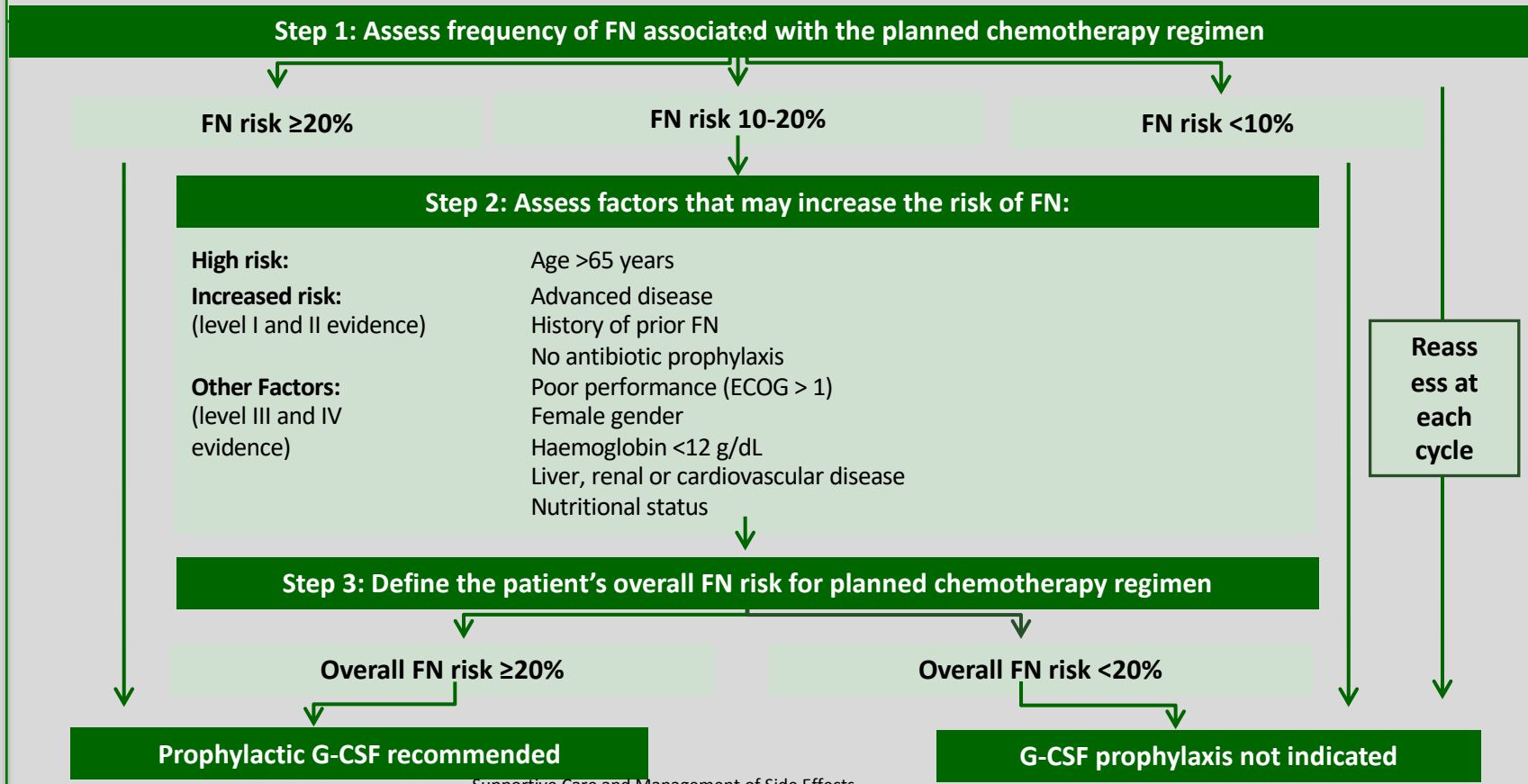
Definition (oral temperature of >38.5°C or two consecutive readings of >38°C for 2 h in a patient with an ANC of <500 cells/mm³ or expected to fall to <500 cells/mm³)

	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	+/-

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



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4. Toxicities/Ovaries

Therapy-associated amenorrhea (CRA, CIA, TIA)	Oxford LoE
▪ CRA may be permanent or temporary (depending on patient age and type of chemotherapy)	2b
▪ The risk of CRA increases with patient 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

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

Guidelines Breast
Version 2021.1E

5. Psychiatric Disorders

- Depression
- Fatigue
- Cognitive impairment
- Sleep disturbances

Guidelines Breast
Version 2021.1E

(Therapy-associated) Depression

	Oxford		
	LoE	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	
▪ Antidepressants have been 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	Oxford 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	+

Guidelines Breast
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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
▪ On aromatase inhibitor therapy, deterioriation of cognitive performance was observed (espec. verbal memory)	1a	B

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(Therapy-associated) Sleep Disturbances

	Oxford		
	LoE	GR	AGO
▪ Sleep disturbances are a common problem in breast cancer patients during and after therapy (20–70%)	2a	B	
▪ Behavioral therapies have 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)**

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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, particularly 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.)	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			
There is no drug-based prophylaxis available			
▪ 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

Guidelines Breast
Version 2021.1E

Cardiotoxicity as Long-term Side Effect

	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, hypercholesterinemia, üre-existing cardiac disease (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: ++

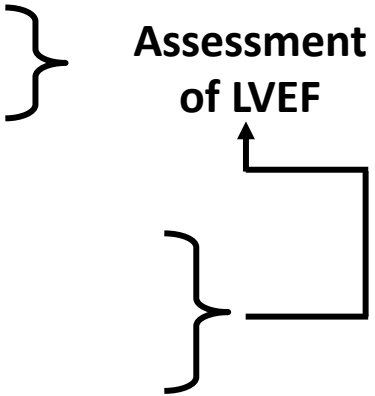
Before start of trastuzumab

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

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

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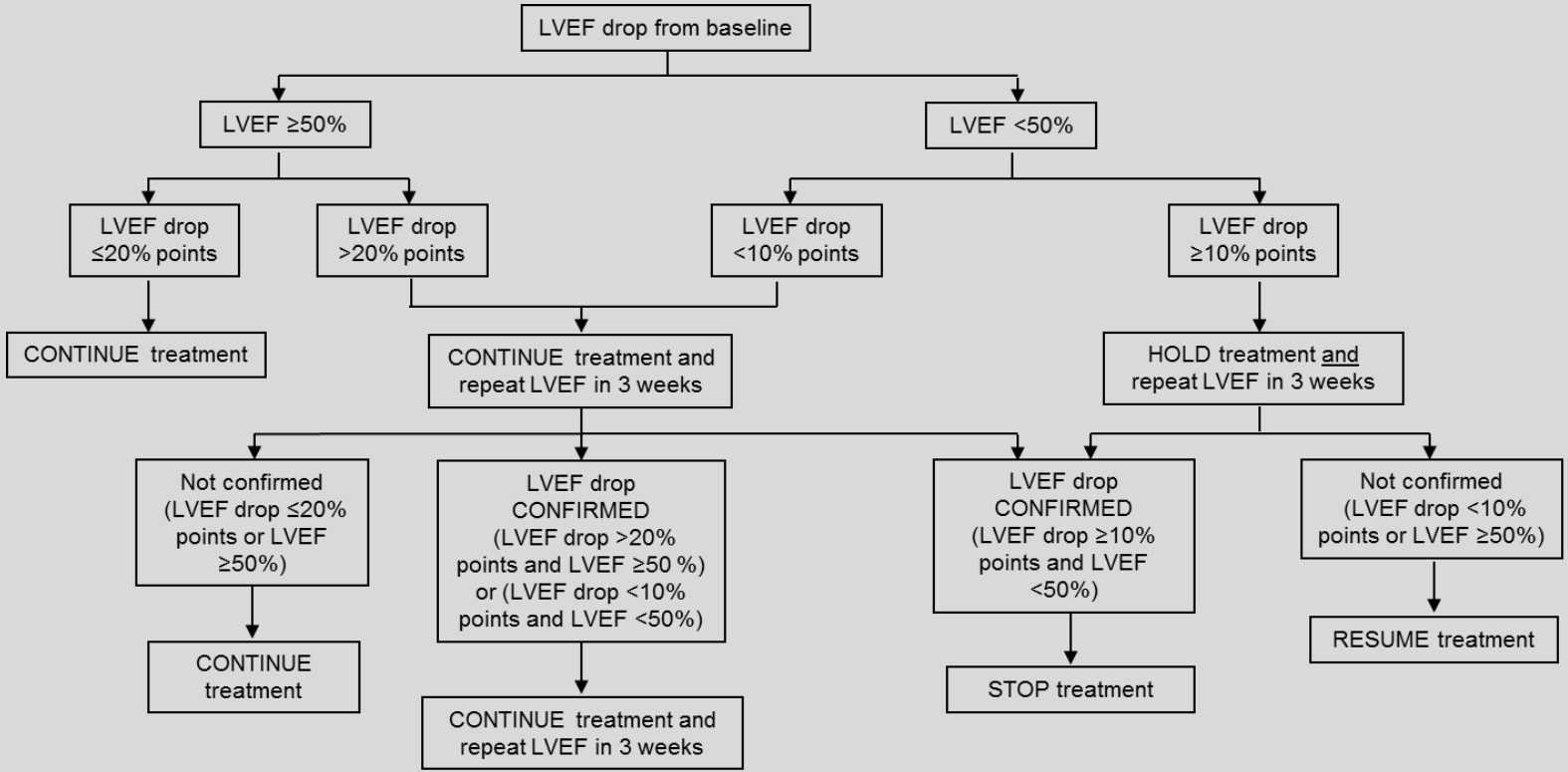

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8. Gastrointestinal Disorders

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

Guidelines Breast
Version 2021.1E

Antiemetic Therapy

http://www.mascc.org/antiemetic-guidelines
www.onkosupport.de

	Oxford		
	LoE	GR	AGO
▪ Prior assessment of emetic potential of chemotherapy protocol	5	D	++
▪ Neurokinin-1-receptor-antagonists	1b	A	++
▪ Dexamethasone (also in chemotherapy combinations with ICPi)	1a	A	++
▪ 5-HT_3-antagonists	1b	A	++
▪ Fixed antiemetic combination therapy	1b	A	++
▪ Rescue Medication			
▪ Olanzapine	1b	A	+
▪ Levomepromazine, benzodiazepines	3b	C	+
▪ Cannabinoids, ginger	3b	C	+

ICPi=Immune Checkpoint inhibitor

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

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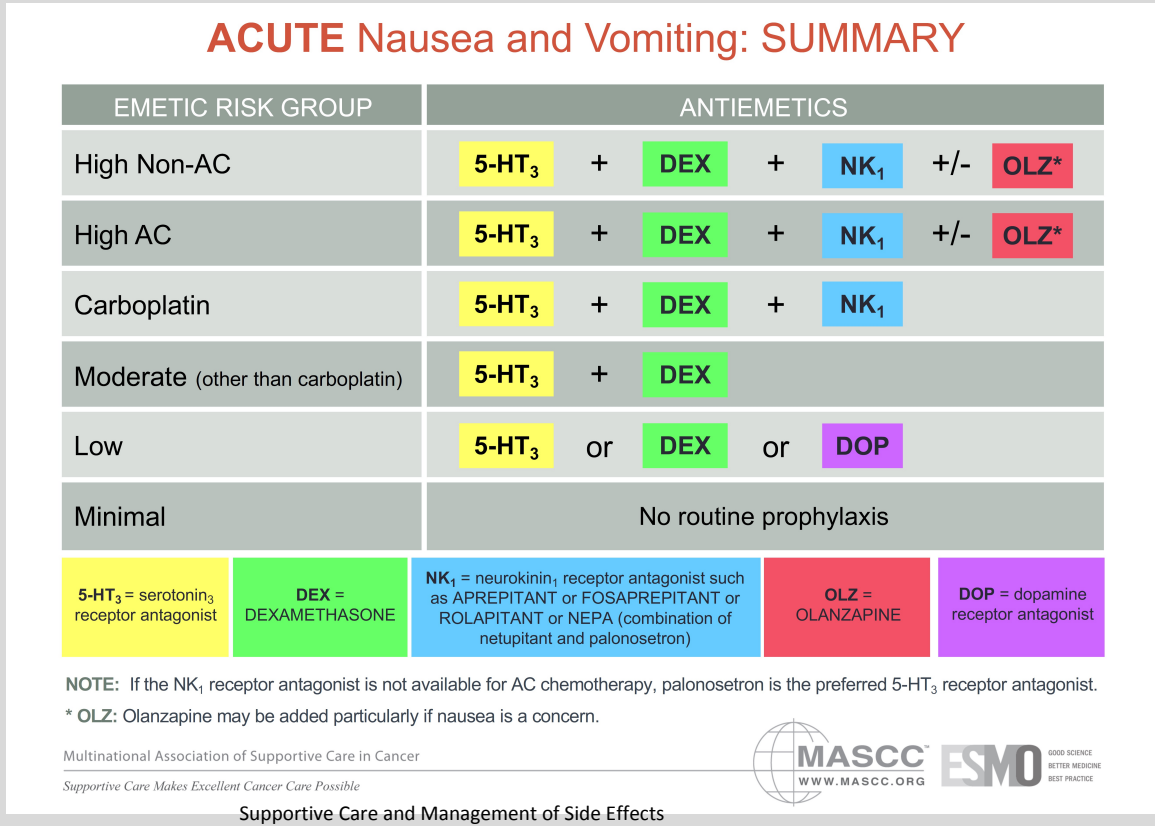

ACUTE Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	5-HT$_3$ + DEX + NK$_1$ +/- OLZ*
High AC	5-HT$_3$ + DEX + NK$_1$ +/- OLZ*
Carboplatin	5-HT$_3$ + DEX + NK$_1$
Moderate (other than carboplatin)	5-HT$_3$ + DEX
Low	5-HT$_3$ or DEX or DOP
Minimal	No routine prophylaxis

5-HT$_3$ = serotonin$_3$ receptor antagonist

DEX = DEXAMETHASONE

NK$_1$ = neurokinin$_1$ receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA (combination of netupitant and palonosetron)

OLZ = OLANZAPINE

DOP = dopamine receptor antagonist

NOTE: If the NK$_1$ receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT$_3$ receptor antagonist.

* **OLZ:** Olanzapine may be added particularly if nausea is a concern.

Multinational Association of Supportive Care in Cancer

Supportive Care Makes Excellent Cancer Care Possible

MASCC WWW.MASCC.ORG ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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

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DELAYED Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	**DEX** or (if APR 125mg for acute: (**MCP** + **DEX**) or (**APR** + **DEX**)) +/- **OLZ***
High AC	NONE or (if APR 125mg for acute: **DEX** or **APR**) +/- **OLZ***
Carboplatin	NONE or (if APR 125mg for acute: **APR**)
Oxaliplatin, or anthracycline, or cyclophosphamide	**DEX** can be considered
Moderate (other)	No routine prophylaxis
Low and Minimal	No routine prophylaxis

DEX = DEXAMETHASONE | **MCP** = METOCLOPRAMIDE | **APR** = APREPITANT | **OLZ** = OLANZAPINE

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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/MukositisGuidelinesMASCC2020(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 toothbrushes**
   - **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

Guidelines Breast
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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 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

Guidelines Breast
Version 2021.1E

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***

Guidelines Breast
Version 2021.1E

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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Version 2021.1E

9. Skin & Subcutaneous Tissue Disorders (Alopecia)

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Version 2021.1E

Skin toxicities

	Oxford		
	LoE	GR	AGO
▪ Avoidance of chemotherapy-induced alopecia by scalp cooling*	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 docetaxel application	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 Meta-analyses: 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	++

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Extravasation of Chemotherapy
Role of Dexrazoxane/Hyaluronic Acid

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**

- **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/