



Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Supportive Therapie und Nebenwirkungsmanagement

Screened data bases

Pubmed 2007 - 2019, ASCO 2010 – 2019, SABCS 2010 – 2019, Cochrane Data Base (2019)

Screened guidelines

1. ABC Consensus Guidelines for Advanced Breast Cancer (ABC 1-4): Cardoso F, Costa A, Senkus E et al. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). Ann Oncol. 2017 Jan 1;28(1):16-33.
2. Thomassen C. et al. ABC5 Consensus: assessment by a German Group of Experts. Breast Care (Basel). 2020
3. ASCO (American Association of Clinical Oncology, Practice Guidelines, 2019) <http://www.asco.org>
4. American Society of Clinical Oncology Clinical Practice Survivorship Guidelines, Endorsements and Adaptations: <https://www.asco.org/practice-policy/cancer-care-initiatives/prevention-survivorship/survivorship-compendium-0>
5. 2016 Updated American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards, Including Standards for Pediatric Oncology: <http://ascopubs.org/doi/pdfdirect/10.1200/JOP.2016.017905>
6. Hershman DL, Lacchetti C, Dworkin RH et al. American Society of Clinical Oncology. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jun 20;32(18):1941-67.
7. NCCN (National Comprehensive Cancer Network , 2019): <http://www.nccn.org>

8. S3-Leitlinie: Supportive Therapie:

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2 – November 2019 AWMF-Registernummer: 032/054OL Zugriff 26.12.2019



Supportive Therapie und Nebenwirkungsmanagement

- **Version 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



• Leitlinien - Umfeld



Leitlinien – Umfeld

Nationale und internationale spezifische Leitlinien befassen sich mit verschiedenen Aspekten der evidenzbasierten supportiven Therapie von Karzinompatientinnen und -patienten

Ohne Anspruch auf Vollständigkeit werden derartige (bes. deutsche) Leitlinienwerke genannt

Hier soll insbesondere auf die Aspekte Wert gelegt werden, die Brustkrebspatientinnen betreffen:

- S3-Leitlinie: Supportive Therapie bei onkologischen Patientinnen
Langversion 1.3 – Februar 2020 AWMF-Registernummer: 032/054OL

1. S3-Leitlinie: Supportive Therapie:

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2 – November 2019 AWMF-Registernummer: 032/054OL Zugriff 26.12.2019

https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.2.pdf



- **Toxizitätsbeurteilung**
 - Akute Toxizität (NCI-CTCAE)
 - Langzeittoxizität (ICPC, ICD-GM)



Toxizitäts-Beurteilung

Akute Toxizität (nach WHO¹ oder NCI-CTC²)

Akute Toxizität nach jedem Therapiezyklus abfragen und dokumentieren		LoE S D AGO ++
Grad	Notwendige Informationen	
0 keine	Beteiligte Organe	
1 mild	Art der Toxizität	
2 mäßig	Zeitintervall nach Behandlung	
3 ausgeprägt	Effekt auf den Allgemeinstatus	
4 lebensbedrohlich	Behandlungsnotwendigkeit	
5 therapiedingter Tod	Erreichen einer Verbesserung	

Langzeittoxizität (=Sekundärerkrankungen nach Tumorthерапie)

Langzeitanalyse und regelmäßige Dokumentation (symptomorientiert nach ICPC³ oder diagnoseorientiert nach ICD-10-GM⁴)

LoE S D AGO ++

Akute Toxizität

1. WHO Handbook for reporting results of cancer treatment, N0 48 (1979) (WHO offset Publications, Geneva)
2. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v5.0 (CTCAE; published 2017);
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 (Download 18.01.2018)

Akute Toxizität nach jedem Therapiezyklus abfragen

1. Cirillo M, Lunardi G, Coati F, et al: Management of oral anticancer drugs: Feasibility and patient approval of a specific monitoring program. *Tumori* 100: 243-248, 2014

Langzeittoxizität

1. International Classification of Primary Care (ICPC) revised December 2016,
<http://www.who.int/classifications/icd/adaptations/icpc2/en/> (Download 18.01.2018) or
<http://www.globalfamilydoctor.com/groups/WorkingParties/wicc.aspx> (Download 18.01.2018)
2. Deutschen Institut für Medizinische Dokumentation und Information (DIMDI), ICD-10-GM Version 2017;
<https://www.dimdi.de/static/de/klassi/icd-10-gm/kodesuche/onlinefassungen/htmlgm2017/> (Download 18.01.2018)
3. Kenyon M, Mayer DK, Owens AK. Late and long-term effects of breast cancer treatment and surveillance management for the general

- practitioner. *J Obstet Gynecol Neonatal Nurs.* 2014 May-Jun;43(3):382-98.
4. Hematopoietic Cell Transplantation Guidelines Taskforce, Auditory and Vision Guidelines Taskforce, Cardiopulmonary Guidelines Taskforce, Endocrine Guidelines Taskforce, Genitourinary and Renal Guidelines Taskforce, Oral, Dental, Gastrointestinal and Hepatic Guidelines Taskforce, et al. Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report. Author manuscript; available in PMC 2017 May 1. Published in final edited form as: *Biol Blood Marrow Transplant.* 2016 May; 22(5): 782–795.
 5. Inge Spronk, Joke C Korevaar, Francois G Schellevis, et al. Evidence-based recommendations on care for breast cancer survivors for primary care providers: a review of evidence-based breast cancer guidelines. *BMJ Open.* 2017; 7(12): e015118.
 6. M.J. Heins, J.C. Korevaar, P.M. Rijken, et al. For which health problems do cancer survivors visit their General Practitioner? *European Journal of Cancer* (2013) 49, 211– 218.



Akute Toxizität (NCI CTCAE vs 5.0, 2017)

(Allgemeine Terminologiekriterien unerwünschter Ereignisse)

- Grad 1
Mild; asymptomatisch oder wenig symptomatisch; lediglich klinische oder diagnostische Beobachtung; eine Intervention ist nicht indiziert.
- Grad 2
Mäßig; minimale, lokale oder nicht-invasive Intervention notwendig; Beeinträchtigung des täglichen Lebens (wie Einkauf, Essenszubereitung etc. (*limiting age-appropriate instrumental ADL**).
- Grad 3
Schwerwiegend oder medizinisch signifikant, aber nicht akut lebensbedrohlich; Klinikaufenthalt oder Verlängerung des Klinik-Aufenthaltes; physisch „außer Gefecht gesetzt“ (*limiting self care ADL***).
- Grade 4
Lebensbedrohliche Folgen; eine Intervention ist dringend notwendig
- Grad 5
Nebenwirkungsbedingter Tod

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.

1. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v5.0 (CTCAE; published 2017);
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 (Download 18.01.2018)



- **Substanzspezifische/Kombinationsspezifische Nebenwirkungen
(teilweise lt. Fachinformationen gemäß MedDRA*)**

* MedDRA - Medical Dictionary for Regulatory Activities

*MedDRA - Medical Dictionary for Regulatory Activities

<https://www.meddra.org/>



Chemotherapie – Akute Toxizitäten I

Substanz	Nebenwirkungsklassen									
	Wiederholend oder kontinuierl. verabreicht, je Mal pro Tag	Wiederholend oder kontinuierl. verabreicht, je Tag	Wiederholend oder kontinuierl. verabreicht, je Woche	Wiederholend oder kontinuierl. verabreicht, je Monat	Psychische Störungen	Störungen des Nervensystems	Allgemeinkr.	Stör. des Kreislaufs und des Verdauungs-	Störungen des Respirations- und Kreislaufsystems	Spättoxizität
Aflatoxin	4	2	0	0	0	-	3	0	2	0
Cyclophosphamid	4	2	0	0	0	-	3	0	2	0
Antimetabolite	4	-	0	0	0	-	3	0	2	0
Methotrexat	5	-	0	0	0	-	3	0	2	0
5-Fluorouracil ^a	5	-	0	0	0	-	3	0	2	0
Capecitabin	4	0 (sehr selten)	0	0	0	-	3	0	2	0
Carboplatin	4	-	0	0	0	-	3	0	2	0
Ketonothalon	4	-	0	0	0	-	3	0	2	0
Platin-Komplexe	4	2	0	0	0	-	3	2	0	0
Cisplatin	4	2	0	0	0	-	3	2	0	0
Carboplatin	4	-	0	0	0	-	3	0	0	0
Antikrebsstoffe / Antiretrovirale	4	-	0	0	0	-	3	0	0	0
Etoposid/Elcosozotolin	5	0	0	0	0-2	-	0-2	0	0	0
Liposomen-Doxorubicin	5	-	0	0	-	0	0	0	0	0
PEG-Hydm. Doxorubicin	4	-	0	0	-	0	0	0	0	0
Doxorubicin	5	0	0	0	0	-	0	0	0	0
Taxane	4	-	0	0	-	0	0	0	0	0
Paclitaxel	5	0	0	0	0	-	0	0	0	0
mito-Paclitaxel	4	-	0	0	-	0	0	0	0	0
Docetaxel	5	-	0	0	-	0	0	0	0	0
Antik. Spindolophilin	4	-	0	0	-	0	0	0	0	0
Vinorelbine nr. (Höd)	4 (sehr selten)	-	0 (sehr selten)	0 (sehr selten)	-	-	0 (sehr selten)	0 (sehr selten)	0 (sehr selten)	0 (sehr selten)

Die Spalte und Klassifizierung der Nebenwirkungen ist nach Nebenwirkungsklassen, Medik. Formulations und den folgenden Häufigkeitskategorien dargestellt:
 0: sehr selten (<1/10.000); 1: selten (2-5/1.000 bis < 1/100.000); 2: Gelegentlich (2-10/1.000 bis < 1/10.000); 3: häufig (2-10/100 bis < 1/10); 4: sehr häufig (2-10/100 bis < 1/10); 5: Nicht bekannt (nurgegen auf Grundlage der verfügbaren Daten nicht abschätzbar).

Nebenwirkungskategorien - MedDRA (Medical Dictionary for Regulatory Activities)

MedDRA: <https://www.meddra.org/> bzw.
https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf

Quellen für die Fachinformationen (Download 19.01.2018)

- Cyclophosphamid: http://www.baxter.de/de_DE/assets/downloads/fachinformation/endoxan.pdf
- Methotrexat: https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation
- 5-Fluorouracil: https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Infusionsloesung-100-ml_546519/fachinformation
- Capecitabin: <https://www.zentiva.de/Produkte/Capecitabin-Zentiva/Downloads?id=a63946ee-51ce-46ac-8184-a468b705ed9b>
- Gemcitabin: <http://www.success-studie.de/b/downloads/Fachinfo/GemzarFI07Jan.pdf>
- Cisplatin: https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-100-ml_543960/fachinformation
- Carboplatin: <http://www.teva.de/index.php?eID=dumpFile&t=f&f=37532&g=1&r=11068%2C11068&token=eebf22e78f1cc8d9935d59c087e80630146f49e>
- Epirubicin:

Doxorubicin:

Liposomales Doxorubicin: https://www.gelbe-liste.de/produkte/Myocet-50-mg-Pulver-Dispersion-u-Loesungsmittel-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsdispersion_359323/fachinformation

PEG-lipo. Doxorubicin: https://www.gelbe-liste.de/produkte/Caelyx-2-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-10-ml_121890/fachinformation

Mitoxantron: https://www.gelbe-liste.de/produkte/Mitoxantron-Teva-2-mg-ml-Injektionsloesung-15ml_543783/fachinformation

Paclitaxel: <https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil>

Nab-Paclitaxel: https://www.gelbe-liste.de/produkte/Abraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension_514889/fachinformation

Docetaxel: <https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d>

Vinorelbine: <http://www.detect-studien.de/dokumente/d3/fachinfo/Navelbine.pdf>

Eribulin: http://www.detect-studien.de/dokumente/d4/fachinfo/Fachinfo_Eribulin_Halaven.pdf

Weitere Referenzen (Auswahl)

1. Azim HA Jr, de Azambuja E, Colozza M, et al.: Long-term toxic effects of adjuvant chemotherapy in breast cancer. Ann Oncol. 2011 Sep;22(9):1939-47.
2. Petrelli F et al: Mortality, leukemic risk, and cardiovascular toxicity of adjuvant anthracycline and taxane chemotherapy in breast cancer: a meta-analysis. Breast Cancer Res Treat. 2012 Sep;135(2):335-46
3. Jim HS et al: Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. J Clin Oncol. 2012 Oct 10;30(29):3578-87
4. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377:914-23
5. Link, H. and S. Schmitz (2013). "Treatment of cancer-associated anaemia: results from a two-day cross-sectional survey in Germany." Onkologie 36(5): 266-272.
6. Fox P, Darley A, Furlong E, et al: The assessment and management of chemotherapy-related toxicities in patients with breast cancer, colorectal cancer, and Hodgkin's and non-Hodgkin's lymphomas: A scoping review. Eur J Oncol Nurs. 2017 Feb;26:63-82. doi: 10.1016/j.ejon.2016.12.008. Epub 2016 Dec 22.
7. Maeda S, Saimura M, Minami S, et al. Efficacy and safety of eribulin as first- to third-line treatment in patients with advanced or

- metastatic breast cancer previously treated with anthracyclines and taxanes. See comment in PubMed Commons below *Breast*. 2017 Jan 2;32:66-72. doi: 10.1016/j.breast.2016.12.017.
- 8. Zhang XH, Hao S, Gao B, et al. A network meta-analysis for toxicity of eight chemotherapy regimens in the treatment of metastatic/advanced breast cancer. *Oncotarget*. 2016 Dec 20;7(51):84533-84543. doi: 10.18632/oncotarget.13023.
 - 9. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of Clinical Oncology* 2011;29:4189- 4198
 - 10. Crawford J.
 - 11. NCCN, editor. NCCNR Practice Guidelines in Oncology - v.1.2011; Myeloid Growth Factors. National Comprehensive Cancer Network 2011. 18-7-2011.
 - 12. Madeddu C, Deidda M, Piras A, et al. Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy. *J Cardiovasc Med (Hagerstown)*. 2016 May;17 Suppl 1 Special issue on Cardiotoxicity from Antiblastic Drugs and Cardioprotection:e12-e18. Review.



Chemotherapie – Akute Toxizitäten II

Medikament	Nebenwirkungsklassen										Beschreibung
	0: Keine Toxizität, Wieder- holbar	1: geringe Toxizität, Wieder- holbar	2: mittlere Toxizität, Wieder- holbar	3: hohe Toxizität, Wieder- holbar	4: sehr hohe Toxizität, Wieder- holbar	5: akute Toxizität, Wieder- holbar	6: akute Toxizität, nicht wieder- holbar	7: sehr akute Toxizität, nicht wieder- holbar	8: tödliche Toxizität, nicht wieder- holbar	9: tödliche Toxizität, nicht wieder- holbar	
Allgemein:										Hypotonie:	
Cyclophosphamid	3	4	4	5	+	5	+	4	5	Makrosomie, Blasen "bladder space"-Funktions- störungen (DPD-Mangel), leicht 5%, schwer >5,1%: Diarrhoe, Herz- Hand-Fuß-Syndrom (HFS), Myokard (DPD-Mangel); Herz- Flut-Erkrankung, Ödem, Herz	
Methotrexat	4	5	5	4	5	5	+	5	5		
5-Fluorouracil	5	5	5	5	+	5	+	5	5		
Capecitabin	4	5	5	5	4	5	+	5	5		
Gemcitabin	5	5	5	5	4	5	+	5	5		
Platin-Karzinoph.:											
Cisplatin	4	5	4	4	+	5	+	5	5	Hämatotoxische, östrogenaktive, CIPN Kotblut, (Hämorrhoiden.)	
Carboplatin	4	5	4	4	4	5	+	4	4		
Antikrebsmittel / Antimetabolite:										Kardiotoxisität (PPE): v.a. Myokarditis, Perikarditis	
Raltitrexed	5	5	5	5	5	5	+	5	5		
Lipos. Glycerofatamin	4	5	4	4	4	5	+	5	5		
PTX-Alpa-Dihydro- Methotrexat	5	5	5	5	5	5	+	5	5		
Taxane											
Paclitaxel	5	5	5	5	5	5	+	5	5	Peripherie Neuropathie (CIPN); Hypertonie, Myalgien	
mito-Paclitaxel	5	5	5	5	5	5	+	5	5	Peripherie Neuropathie (CIPN)	
Docetaxel	5	5	5	5	5	5	+	5	5	Fluid retentions, Paroxysmische, Kotblut, Myalgia	
Andere Krebstherapie:										Phlebitis, GU-Trauma (HFS), CIPN: Überwärmung, CIPN	
Vorozostatin IV (HFS)	500	2.000	100	2.000	500	2.000	+	5	5		
Gelfoam	5	5	4	4	4	5	+	5	5		

Die Güte und Grobulation der Nebenwirkungen ist nach Nebenwirkungsklassen, MedDRA-Terminologie und den folgenden Häufigkeitskategorien dargestellt:
1: Sehr selten (>1/10.000); 2: Selten (2/1.000 bis > 1/10.000); 3: Gelegentlich (1/100.000 bis < 1/10.000); 4: Häufig (3/1.000 bis < 1/100); 5: Sehr häufig (> 1/100).
Nicht bekannt (Häufigkeit auf Grundlage der verfügbaren Daten nicht abschätzbar).

Abkürzungen

AML = Akute myeloische Leukämie; DPD = Dihydropyrimidin-Dehydrogenase); CHF = Kardiomyopathie; CIPN = Chemotherapie induzierte periphere Neuropathie; HFS = Hand-Fuß-Syndrom; PPE = Palmares und plantares Erythem.

Nebenwirkungskategorien - MedDRA (Medical Dictionary for Regulatory Activities)

MedDRA: <https://www.meddra.org/> bzw.

https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf

Quellen für die Fachinformationen (Download 19.01.2018)

Cyclophosphamid: http://www.baxter.de/de_DE/assets/downloads/fachinformation/endoxan.pdf

Methotrexat: https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation

5-Fluorouracil: https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionslösung-100-ml_546519/fachinformation

Capecitabin: <https://www.zentiva.de/Produkte/Capecitabin-Zentiva/Downloads?id=a63946ee-51ce-46ac-8184-a468b705ed9b>

Gemcitabin: <http://www.success-studie.de/b/downloads/Fachinfo/GemzarFI07Jan.pdf>

Cisplatin: <https://www.gelbe-liste.de/produkte/Cisplatin-Teva-1-mg-ml-Konzentrat-zur-Herstellung-einer->

Infusionsloesung-100-ml_543960/fachinformation

Carboplatin: <http://www.teva.de/index.php?eID=dumpFile&t=f&f=37532&g=-1&r=11068%2C11068&token=eebf22e78f1cc8d9935d59c087e80630146f49e>

Epirubicin:

Doxorubicin:

Liposomales Doxorubicin: https://www.gelbe-liste.de/produkte/Myocet-50-mg-Pulver-Dispersion-u-Loesungsmittel-fuer-ein-Konzentrat-zur-Herstellung-einer-Infusionsdispersion_359323/fachinformation

PEG-lipo. Doxorubicin: https://www.gelbe-liste.de/produkte/Caelyx-2-mg-ml-Konzentrat-zur-Herstellung-einer-Infusionsloesung-10-ml_121890/fachinformation

Mitoxantron: https://www.gelbe-liste.de/produkte/Mitoxantron-Teva-2-mg-ml-Injektionsloesung-15ml_543783/fachinformation

Paclitaxel: <https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil>

Nab-Paclitaxel: https://www.gelbe-liste.de/produkte/Abraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension_514889/fachinformation

Docetaxel: <https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d>

Vinorelbine: <http://www.detect-studien.de/dokumente/d3/fachinfo/Navelbine.pdf>

Eribulin: http://www.detect-studien.de/dokumente/d4/fachinfo/Fachinfo_Eribulin_Halaven.pdf

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3. Jim HS et al: Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. J Clin Oncol. 2012 Oct 10;30(29):3578-87
4. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377:914-23
5. Link, H. and S. Schmitz (2013). "Treatment of cancer-associated anaemia: results from a two-day cross-sectional survey in Germany." Onkologie 36(5): 266-272.

6. Fox P, Darley A, Furlong E, Miaskowski C, Patiraki E, Armes J, Ream E, Papadopoulou C, McCann L, Kearney N, Maguire R. The assessment and management of chemotherapy-related toxicities in patients with breast cancer, colorectal cancer, and Hodgkin's and non-Hodgkin's lymphomas: A scoping review. *Eur J Oncol Nurs.* 2017 Feb;26:63-82. doi: 10.1016/j.ejon.2016.12.008. Epub 2016 Dec 22.
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8. Zhang XH, Hao S, Gao B, et al. A network meta-analysis for toxicity of eight chemotherapy regimens in the treatment of metastatic/advanced breast cancer. *Oncotarget.* 2016 Dec 20;7(51):84533-84543. doi: 10.18632/oncotarget.13023.
9. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of Clinical Oncology* 2011;29:4189- 4198
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Endokrine Therapie – Toxizitäten

Substanz	Schwangerschaft		Laktation und postmenopausal		Hochdosis mit Megadosen		Haut / Lippenstift		Immunosuppression, Zytostatika		Endokrine Toxizitäten		Endokrinal und Krebsprädisposition		Metastasierung des Tumors		Augenschwund		Effekt des Osteo- und Myelotoxiszitäts		Kontrazeption (bei Antiestrogen)	
	WHO	ATC	WHO	ATC	WHO	ATC	WHO	ATC	WHO	ATC	WHO	ATC	WHO	ATC	WHO	ATC	WHO	ATC	WHO	ATC	WHO	
AIKON																						
Tamoxifen	-	A1	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	
All																						
Anastrozol	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	
Exemestan	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	
Letrozol	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	

Fulvestrant	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	C02	-	

Hinweisungen, zentrale Endokrinopathie (z.B. Hypothalamus)

Hinweise auf Nebenwirkungen (nach Systemorganklassen, Medikament-Terminologie und den folgenden Häufigkeitskategorien dargestellt):

b) sehr selten (<1/10.000); c) selten (2/1.000 bis < 1/100.000); d) Gelegentlich (1/1.000 bis < 1/100); e) häufig (2/1.000 bis < 1/10); f) sehr häufig (≥ 1/10).

– Nicht bekannt (ausgeführt auf Grundlage der verfügbaren Daten nicht abschätzbar)

Nebenwirkungskategorien - MedDRA (Medical Dictionary for Regulatory Activities)

MedDRA: <https://www.meddra.org/> bzw.

https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf

Quellen für die Fachinformationen (Download 19.01.2018)

Tamoxifen: https://www.gelbe-liste.de/produkte/Tamoxifen-20-mg-HEXAL-Filmtbl_8660/fachinformation

Anastrozol: <https://imedikament.de/anastrozol-ratiopharm-1-mg-filmtabletten/fachinformation>

Exemestan: http://www.success-studie.de/c/downloads/Fachinfo/Fl_ExemestanAromasin.pdf

Letrozol: http://www.success-studie.de/b/downloads/Fachinfo/Femara_Juli_2014.pdf

Fulvestrant: https://www.gelbe-liste.de/produkte/Fulvestrant-HEXAL-250-mg-Injektionsloesung-in-einer-Fertigspritze_912622/fachinformation



Nebenwirkungen – Antikörper/ Antikörper-Wirkstoff-Konjugate

	Oxford	
	LoE	GR
Trastuzumab		
▪ Kardiotoxizität in der adjuvanten Therapie (1,0–2,0%)	3b	A
▪ Tropponin I als Marker für Kardiotoxizität	3b	B
Pertuzumab		
▪ Ekzem, Diarrhoe, Mukositis	3b	A
Trastuzumab-Emtansin (T-DM1)		
▪ Thrombozytopenie, Anstieg Leberenzyme Fieber, Kopfschmerzen, Pneumonitis, Polyneuropathie	3b	A
Bevacizumab		
▪ Hypertonus, Linkaventrikuläre Dysfunktion Blutung, Proteinurie	1a	A
Trastuzumab-Deruxtecan		
▪ Interstitielle Lungenerkrankung, Neutropenie, Übelkeit	3b	B

Cardiotoxicity....

1. Slamon D, Eiermann W, Robert N et al: Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 365:1273-1283, 2011
2. Procter M, Suter TM, de Azambuja, et al: Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. *J Clin Oncol* 28: 3422-3428, 2010
3. Russell SD, Blackwell KL, Lawrence J, et al: Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. *J Clin Oncol* 28: 3416-3421, 2010
4. Higa GM, Abraham J: Biological mechanisms of bevacizumab-associated adverse events. *Expert Rev Anticancer Ther* 2009;9:999–1007
5. Martin M, Esteva FJ, Alba E, et al: Minimizing cardiotoxicity while optimizing treatment efficacy with trastuzumab: review and expert recommendations. *Oncologist* 2009;14:1–11
6. Untch M, Eidtmann H, du Bois A, et al: Cardiac safety of trastuzumab in combination with epirubicin and cyclophosphamide in women with metastatic breast cancer: results of a phase I trial. *Eur J Cancer* 2004; 40:988–97
7. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al.: Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet*. 2017 Mar 25;389(10075):1195-1205.

8. Pondé NF, Lambertini M, de Azambuja E. Twenty years of anti-HER2 therapy-associated cardiotoxicity. *ESMO Open*. 2016 Jul;1(4):e000073.

Troponin I....

1. Cardinale D, Colombo A, Torrisi R, et al: Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. *J Clin Oncol* 28: 3910-3916, 2010

Bevacizumab

1. Cortes J, Calvo V, Ramirez-Merino N et al: Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: a metanalysis. *Ann Oncol*. 2019 Jan 9. doi: 10.1093/annonc/mdy535
2. Hamilton EP, Blackwell KL: Safety of Bevacizumab in patients with metastatic breast cancer. *Oncology* 80:314-325, 2011
3. Syrigos KN, Karapanagiotu E, Boura P et al: Bevacizumab-induced hypertension. *Biodrugs*; 25:159-169, 2011
4. Blowers E, Hall K: Managing adverse events in the use of bevacizumab and chemotherapy. *Br J Nurs* 2009;18:351-6, 58
5. Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 357: 2666-2676, 2007

Lapatinib...

1. Wu PA, Balagula Y, Lacouture ME, et al.: Prphylaxis and treatment of dermatologic adverse events from epidermal growth factor receptor inhibitors. *Curr Opin Oncol* 23:343-351, 2011
2. Von Minckwitz G, Eidtmann H, Loibl S et al: Integrating bevacizumab, everolimus, and lapatinib into current neoadjuvant chemotherapy regimen for primary breast cancer. Safety results of the GeparQuinto trial. *Ann Oncol* 22:301-306, 2011
3. Sherill B, Amonkar MM, Sherif B et al: Quality of life in hormone receptor-positive Her2-positive metastatic breast cancer patients during treatment with letrozole alone or in combination with lapatinib. *Oncologist* 15:944-953, 2010
4. Cameron D, Casey M, Olica C et al: Lapatinib plus capecitabine in women with Her2-positive advanced breast cancer: Final survival analysis of a phase III randomized trial. *Oncologist* 15:924-934, 2010
5. Geyer CE, Forster J, Lindquist D; et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 355:2733-2743, 2006

Pertuzumab

1. von Minckwitz G, Procter M, de Azambuja E, et al. APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER-2 Positive Breast Cancer. *N Engl J Med.* 2017 Jul 13;377(2):122-131.
2. Drucker AM, Wu S, Dang CT, et al.: Risk of rash with the anti-HER2 dimerization antibody pertuzumab: a meta-analysis. *Breast Cancer Res Treat.* 2012 Sep;135(2):347-54.
3. Baselga J, Cortes J, Kim S-B et al. Pertuzumab plus Trastuzumab plus Docetaxel for metastatic breast cancer. *N Engl J Med* 2012; 366:109-119

T-DM1

1. Verma S, Miles D, Gianni L, et al: EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012 Nov 8;367(19):1783-91.
2. von Minckwitz G, Huang CS, Mano MS, et al.; KATHERINE Investigators. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med.* 2018 Dec 5. doi: 10.1056/NEJMoa1814017

Trastuzumab-Deruxtecan

1. Modi S, Saura C, Yamashita T, et al.: Trastuzumab deruxtecan in previously treated her2-positive breast cancer. *N Engl J Med* 2019.
2. Tamura K, Tsurutani J, Takahashi S, et al.: Trastuzumab deruxtecan (ds-8201a) in patients with advanced her2-positive breast cancer previously treated with trastuzumab emtansine: A dose-expansion, phase 1 study. *Lancet Oncol* 2019;20:816-826.

Nebenwirkungen antiHER2-TKI: Neratinib, Lapatinib



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Lapatinib

UE, %	All Grade	Grad >/=3
Diarhöe	62%	6%
Nausea	38%	4%
Hautausschlag	60%	6%
Fatigue	36%	4%
Kardiale NW	3%	< 1% SAE
Hepatobiliäre NW	8%	
Alle UE	92%	SAE 6%

Neratinib

UE, %	All Grade (%)	Grad >/=3 (%)
Diarhöe	90	46,1
Nausea	43	2
Bauchschmerzen	36	2
Fatigue	27	2
Erbrechen	26	3
Hautausschlag	18	0,6
Stomatitis	14	0,6
Appetithunger	12	0,2
Dyspepsie	10	0,4
ALAT-Erhöhungen	9	1,2
ASAT-Erhöhungen	7	0,7
Nagelstörungen	8	0,3
Trockene Haut	6	0

Primäre Prophylaxe mit
Loperamid

LoE GR AGO
2b **B** **++**

- Chan A, Delaloge S, Holmes FA et al Neratinib after trastuzumab –based adjuvant therapy in patients with HER2 positive breast cancer (ExteNET): a multicentre, randomized, double-blind, placebo controlled , phase III trial. Lancet Oncol 17(39): 367-377, 2016
- Piccart-Gebhart M , Holmes E., Baselga J et al Adjuvant Lapatinib and Trastuzumab for Early Human Epidermal Growth Factor Receptor 2-positive Breast Cancer:Results From the Randomized Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial. JCO 34:1034-1042, 2015
- Neratinib: FDA Produktinformation 2017



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Nebenwirkungen anti-HER2 TKI Tucatinib+ Trastuzumab+ Capecitabin

NW	Alle Grade (%)	≥ Gad 3 (%)
Alle Ereignisse	99.3	55.2
Diarrhoe	80.9	12.9
PPE Syndrom	63.4	13.1
Übelkeit	58.4	3.7
Fatigue	45.0	4.7
Erbrechen	35.9	3.0
Stomatitis	25.5	2.5
Red. Appetit	24.8	0.5
Kopfschmerz	21.5	0.5

1. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, Lin NU, Borges V, Abramson V, Anders C, Bedard PL, Oliveira M, Jakobsen E, Bachelot T, Shachar SS, Müller V, Braga S, Duhoux FP, Greil R, Cameron D, Carey LA, Curigliano G, Gelmon K, Hortobagyi G, Krop I, Loibl S, Pegram M, Slamon D, Palanca-Wessels MC, Walker L, Feng W, Winer EP. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. *N Engl J Med.* 2020 Feb 13;382(7):597-609. doi: 10.1056/NEJMoa1914609. Epub 2019 Dec 11.



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UE, %	Alle Grade	Grad 3	Grad 4
Neutropenie	79,3/74,3/71,3	56,1/49,7/39,6	39,4/34,4/13,3
Leukopenie	38,4/32,3/20,8	34,1/13,6/7,3	6,2/3,2/0,3
Anämie	24,5/20,4/20,4	5,2/6,3/5,8	6,3/5,3/0
Thrombozytopenie	15,3/11,7/10,8	1,4/0,6/2,0	8,2/0/1,0
Fatigue	37,4/36,3/36,1	1,8/0,3/1,8	6,9/3,0
Übelkeit	35,3/31,5/38,5	9,2/0,4/0,9	8,9/0
Stomatitis	15,8/20,3/20,4	9,3/3,6/3,2	8,7/0
Diarhoe	26,1/21,0/21,3	1,6/1,3/0,5	2,4/0
Alopezie	32,8/33,2/26,6	-	-
Exanthem	17,6/17,1/14,0	0,9/0,6/1,6	8,7/0
ALT Erhöhung	9,9/15,6/15,6	1,7/1,3/0,8	6,3/1,4/0,8
AST Erhöhung	9,7/13,0/15,0	2,5/3,6/0,0	6,7/3,0
Infiltrationen	44/50,3/39,1	6,0/7,4/4,0	3,7/4,0/0,9
QT Prolongation	N.A./7,5/N.A.	N.A./0,3/N.A.	N.A./0/N.A.
Palbociclib/Ribociclib/Abemaciclib			

Palbociclib

- Verma S, Bartlett CH, Schnell P, et al. Palbociclib in Combination With Fulvestrant in Women With Hormone Receptor-Positive/HER2-Negative Advanced Metastatic Breast Cancer: Detailed Safety Analysis From a Multicenter, Randomized, Placebo-Controlled, Phase III Study (PALOMA-3). *Oncologist*. 2016 Oct;21(10):1165-1175. Epub 2016 Jul 1.
- N.Harbeck, J. Ettl, Palbociclib, CDK 4 / 6 Inhibition als neue Therapieoption bei Patientinnen mit fortgeschrittenem HR+/ Her – Mammakarzinom. Drug Report, 2017

Ribociclib

- Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med*. 2016 Nov 3;375(18):1738-1748. Epub 2016 Oct 7.

Abemaciclib

- Sledge GW, Jr., Toi M, Neven P, et al: Monarch 2: Abemaciclib in combination with fulvestrant in women with hr+/her2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol* 2017;35:2875-2884.
- Goetz MP, Toi M, Campone M, et al: Monarch 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* 2017;35:3638-3646.



QT-Zeit-Verlängerung: Ribociclib vs Placebo

- Post-baseline Verlängerung der QT-Zeit > 480 msec 6.9% vs 1.2 %
- Post-baseline Verlängerung der QT Zeit > 500 msec 1,5 % vs 0,3%
- Therapieabbruch wegen QT Zeit Verlängerung 0.3% vs 0.6%
- QT Verlängerung ist nicht mit klinischer Symptomatik assoziiert, aber mit einem erhöhten Risiko für lebensbedrohliche Arrhythmien („torsades de pointes“, TdP)

1. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomized phase 3 trial. Lancet Oncol. 2018 Jul;19(7):904-915.
2. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone-Receptor-Positive, Human Epidermal Growth Factor Receptor-2 Negative Advanced Breasts Cancer: MONALEESA-3. J Clin Oncol. 2018 Aug 20;36(24):2465-2472.
3. Durairaj C, Ruiz-Garcia A, Gauthier ER, et al. Palbociclib has no clinically relevant effect on the QTc interval in patients with advanced breast cancer. Anticancer Drugs. 2018 Mar;29(3):271-280.
4. Trinkley KE, Page RL 2nd, Lien H, et al. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. Curr Med Res Opin. 2013 Dec;29(12):1719-26.

Nebenwirkungen mTOR-Inhibitor (Everolimus)

NE, %	Alle Grade (%)	Grad 3/4 (%)
Stomatitis	11,8	1,8
Ausschlag	7,4	0,0
Anämie	3,3	1,8
Fatigue	3,0	0,0
Übelkeit	3,0	0
Erbrechen	2,9	0
Darmfet	6,2	0,0
Appetitminderung	4,0	0,0
Kopfschmerz	3,9	0
Gewichtsverlust	3,8	0
Dyspnoe	3,8	0,0
Arthralgie	3,3	0
Epilepsie	3,1	0
Delir	3,0	0
Osteoporose	3,0	0
Parese	2,9	0
Husten	4,1	0
ALZ Erhaltung	2,8	0
Pneumonitis	0,2	0
Katharose	2,4	0,0
Dysgeusie	4,3	0

1. Baselga J, Campone M, Piccart M et al Everolimus in postmenopausal hormone receptor positive advanced breast cancer N Engl J Med:366,: 520 -529, 2012



Nebenwirkungen PIK3CA in Kombination mit endokriner Therapie

Alpelisib+Fulvestrant

UE, %	All Grade	Grad >/=3
Hyperglykämie	63,7%	32,7%
Diaröhö	57,7%	6,7%
Übelkeit	44,7%	2,3%
Appetitlosigkeit	35,6%	< 1% SAE
Hautausschlag	35,5%	9,9%
Erbrechen	27,1%	< 1% SAE
Gewichtsverlust	26,8%	3,8%
Stomatitis	24,6%	2,3%
Fatigue	24,3%	3,5
Asthenie	20,4%	1,8
Haarverlust	19,7%	0
Mucositis	18,9%	2,3

Berücksichtigung der Empfehlungen
zum Nebenwirkungsmanagement
(Diabetes mellitus, Hyperglykämie,
Insulinresistenz und metabolisches
Syndrom)

LoE	GR	AGO
2b	B	++

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

1. H. S. Rugo, F. André, et al. Time Course and Management of Key Adverse Events During the Randomized Phase 3 SOLAR-1 Study of PI3K inhibitor Alpelisib Plus Fulvestrant in Patients With HR-Positive Advanced Breast Cancer in press, 2020
2. Andre F, Ciruelos E, Rubovszky G et al.:Alpelisib for pik3ca-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019;380:1929-1940.
3. Mayer IA, Abramson V, Formisano L, et al.: A phase ib study of alpelisib (byl719), a pi3kalpha-specific inhibitor, with letrozole in er+/her2-negative metastatic breast cancer. Clin Cancer Res 2016.

Nebenwirkungen PARP-Inhibitoren – Olaparib, Talazoparib

Olaparib			Talazoparib		
UE, %	Allg. Grade (%)	Grad 3/4 (%)	UE, %	Allg. Grade (%)	Grad 3/4 (%)
Jugliche UE	97,3	36,4	Jugliche UE	94,6	31,8
Neutropenie	29,8	9,3	Neutropenie	34,6	30,9
Anämie	40,0	16,1	Anämie	52,8	39,2
Fatigue	28,0	2,9	Fatigue	50,3	1,7
Übelkeit	58,0	0	Übelkeit	48,6	0,3
Erbrechen	29,8	0	Erbrechen	34,8	2,4
Diarrhoe	29,0	0,3	Diarrhoe	33,8	0,7
Appetitminderung	16,1	0	Appetitminderung	21,3	0,3
Kopfschmerz	20,0	1	Kopfschmerz	32,5	1,7
Pynore	14,1	0	Pynore	21,0	2,6
Husten	17,1	0	Husten	37,5	2,4
ALT Erhöhung	15,3	1,5	ALT Erhöhung	3,1	1,7
AST Erhöhung	9,3	2,4	AST Erhöhung	1,4	0,3
PPI	0,5		PPI	98,6	31,8
Therapieabbruch	4,9		Therapieabbruch	34,6	26,9

1. Litton JK, Rustin HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018 Aug 23;379(8):753-763.
2. Robson M, Im SA, Senkus E et al. Olaparib for metastatic breast cancer in patients with germline BRCA mutation N Engl J Med 377: 523-533, 2017

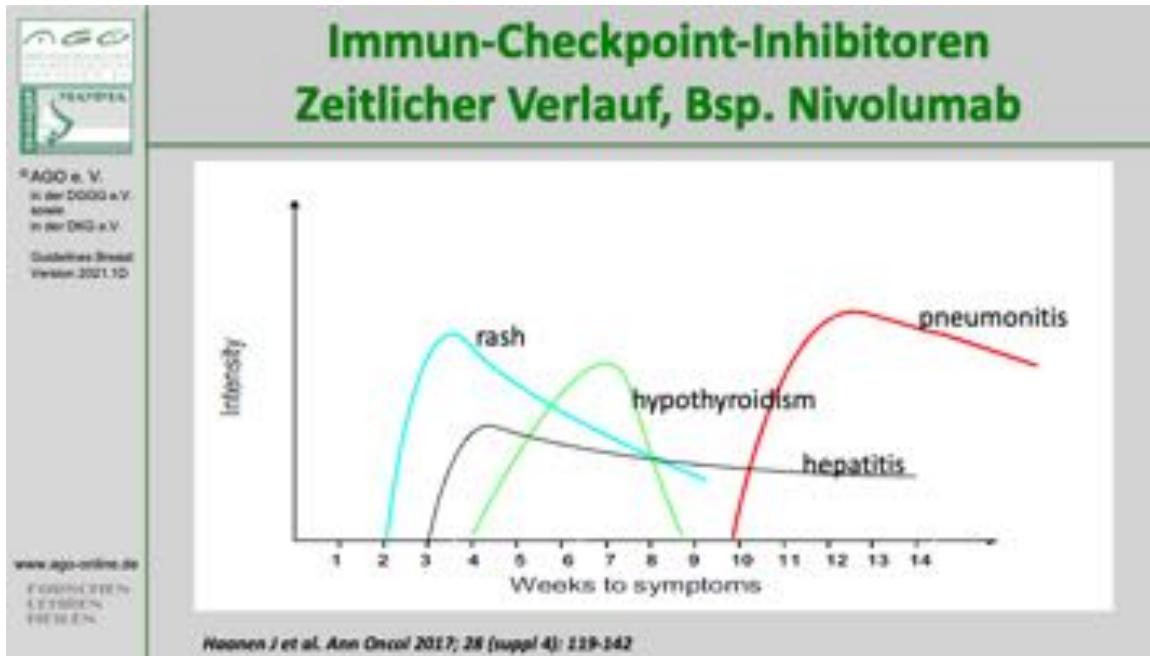


Immun-Checkpoint-Inhibitoren

- Therapeutische Ansätze (Antikörper)

- PD1 /PD-L1
 - PD1
 - Nivolumab
 - Pembrolizumab
 - PD-L1
 - Atezolizumab
 - Durvalumab
 - Avelumab

1. Haanen J, Carbonnel F, Robert C, et al, on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelöines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142. doi: ^0.1093/annonc/mdx225
2. Ingrid A. Mayer¹, Aleix Prat², Daniel Egle³, et al.: A Phase II Randomized Study of Neoadjuvant Letrozole Plus Alpelisib for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer (NEO-ORB) Clin Cancer Res. 2019 May 15; 25(10): 2975–2987.



1. Haanen J, Carbonnel F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142.



Immun-Checkpoint-Inhibitoren

- Nebenwirkungen ≥ Grad 3

- Diarrhoe
- Fatigue
- Hautveränderungen (v.a. makulopapulöses Exanthem, Vitiligo, Epidermolysen)
- Pneumonitis
- Colitis
- Hypophysitis
- Hepatitis
- Nephritis
- Thyreoiditis (Hyper-/Hypothyreose)
- Guillain-Barré-Syndrom
- Kardiomyopathie
- Myopathie – Myalgie – Rhabdomyolyse
- Uveitis

1. Haanen J, Carbonnel F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142.

Immun-Checkpoint-Inhibitoren Toxizitäten (Gesamt in %)

	Atezolizumab	Nivolumab	Pembrolizumab
Diarrhö	18,6%	13%	18%
Kolitis	1,1%	2%	1%
Hautausschlag	18,6%	15%	<1%
Hepatotoxizität	0,3%	1%	0,5%
Hypophysitis	<0,1%	<1%	0,5%
Pneumonitis	3,1%	3%	2,9%
Schilddrüsens- fehlfunktion	Hyper- 1,7% Hypo- 4,7%	Hyper- 1% Hypo- 4%	Hyper- 1,2% Hypo- 8,3%
Nephritis	<1%	1%	0,7%
Neuropathien	0,2%	<1%	<1%

Atezolizumab Fachinformationen 2018, Nivolumab, safety management BMS 2014, Pembrolizumab PI 2014

Atezolizumab: <https://www.fachinfo.de/suche/fi/021700>

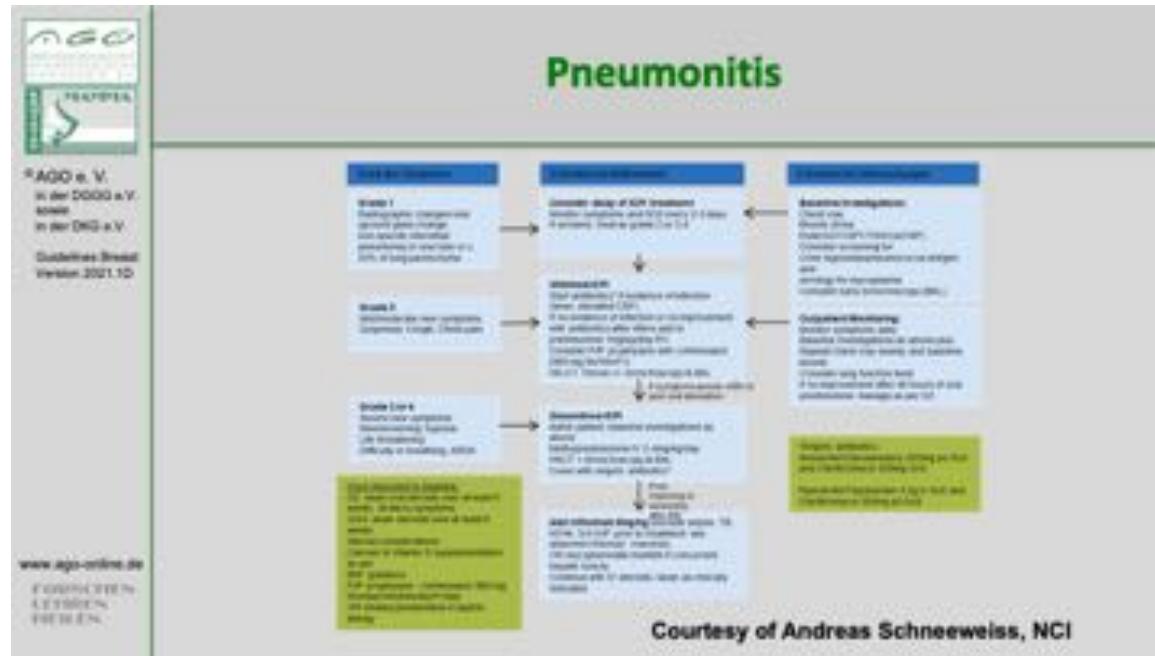
Nivolumab: <https://www.fachinfo.de/suche/fi/020675>

Pembrolizumab: <https://www.fachinfo.de/suche/fi/020716>

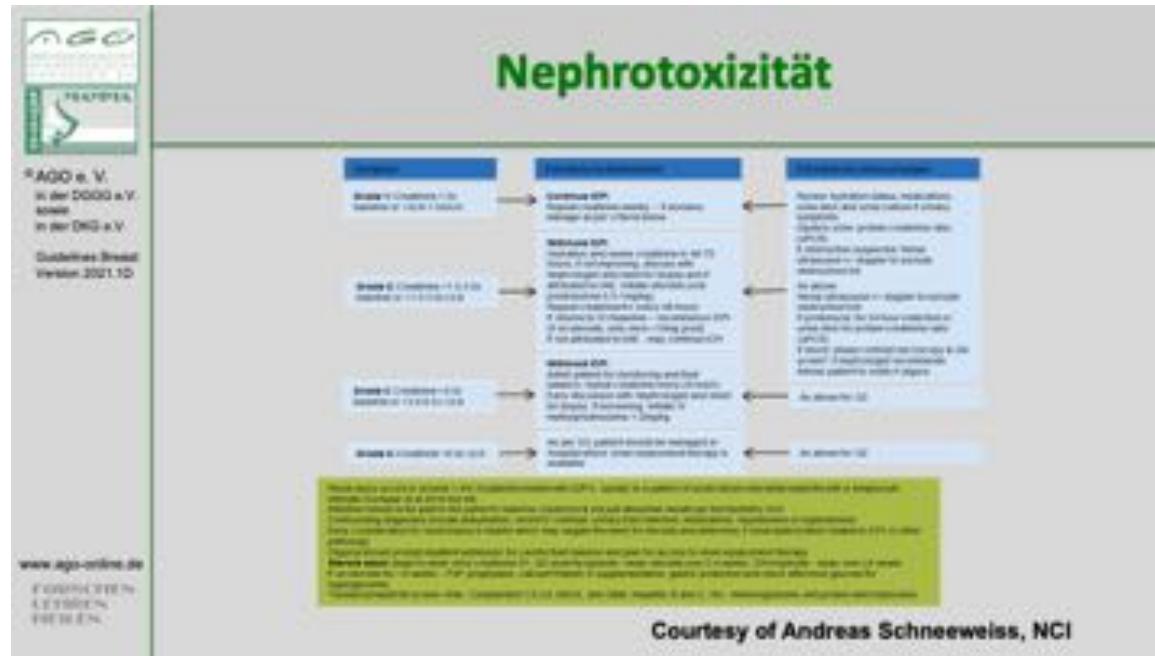
Immun-Checkpoint-Inhibitoren NW-Management - Grundsätze

CTC AE-Grad	Management
1	<ul style="list-style-type: none"> ▪ Supportive Therapie ▪ Engmaschige Kontrollen ▪ Ausschluss Infektion ▪ Patientenaufklärung
2	<p>Wie Grad 1 aber</p> <ul style="list-style-type: none"> ▪ Pausierung der Therapie bis alle iAE Grad 0-1 ▪ Ggf Kortikosteroide
3	<ul style="list-style-type: none"> ▪ Supportive Therapie ▪ I. v.-Steroide (z. B. 1-2 mg/kg Prednisolon) <p>Wenn keine Besserung innerhalb 48 h:</p> <ul style="list-style-type: none"> ▪ Ggf zusätzliche andere Immunsuppression (Inflamimab, MMF) ▪ Ggf organspezifische weitere Diagnostik (z. B. Koloskopie) ▪ Ggf Konsil Fachspezialist ▪ Ausschluss oder Behandlung von Infektion ▪ Absetzen der Therapie, ggf Fortsetzung, wenn CTC AE Grad 0,1 ▪ Langarmes Ausschleichen der Steroide (3-6 Wochen)
4	Wie Grad 3 aber dauerhaftes Absetzen der Therapie

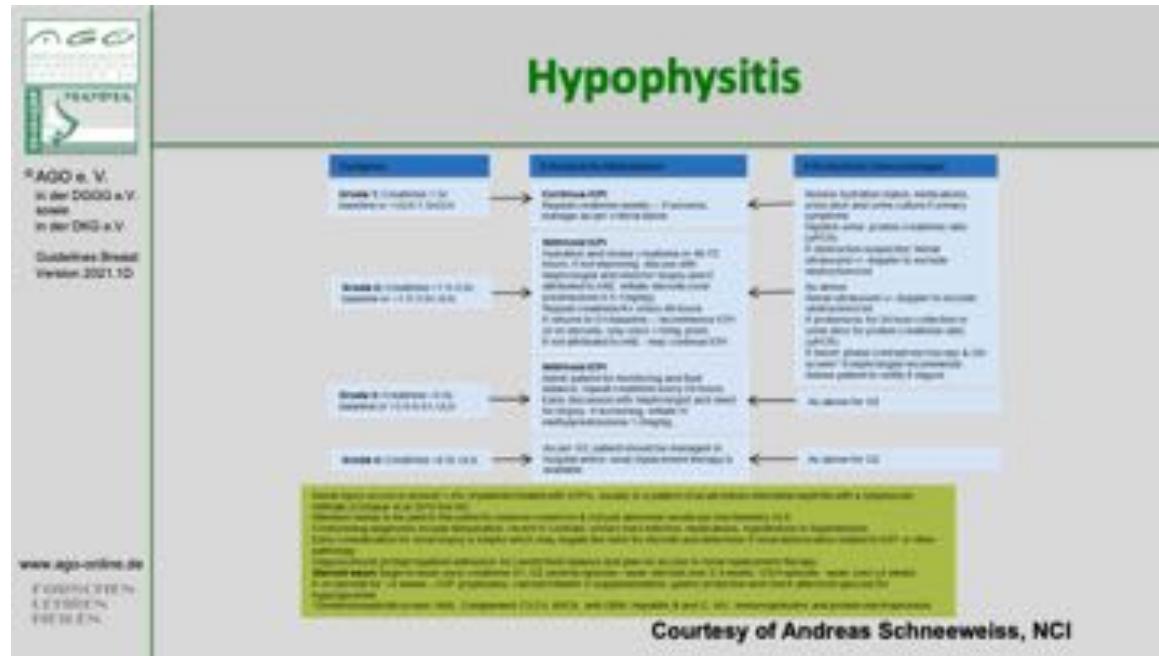
1. Haanen J, Carbonnel F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142.



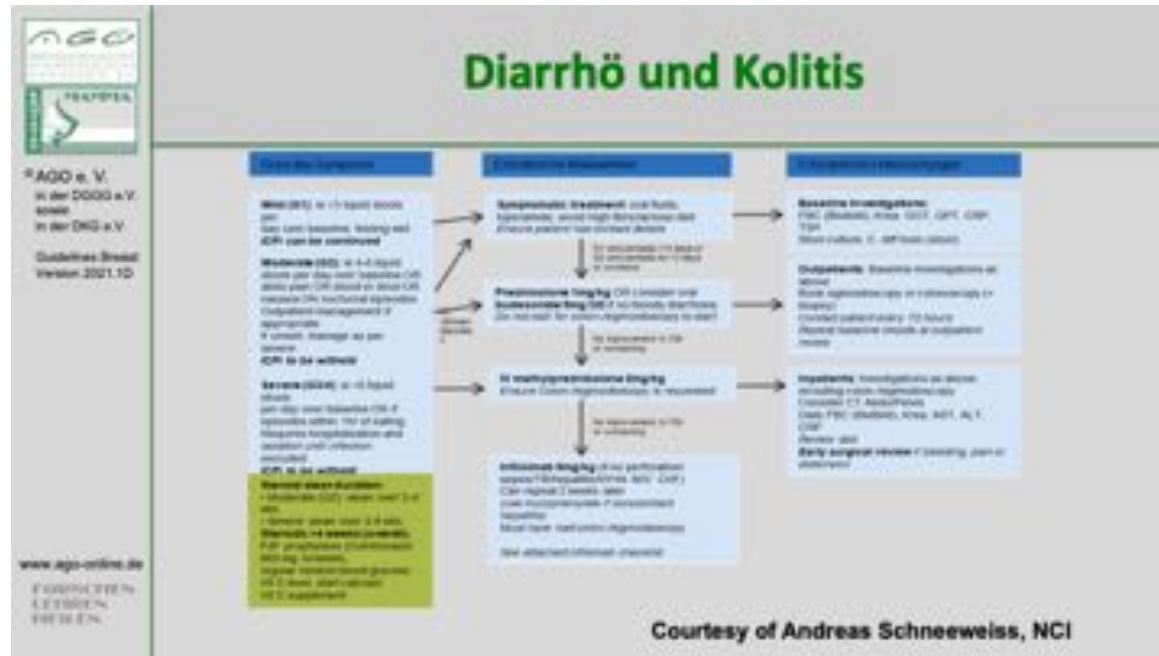
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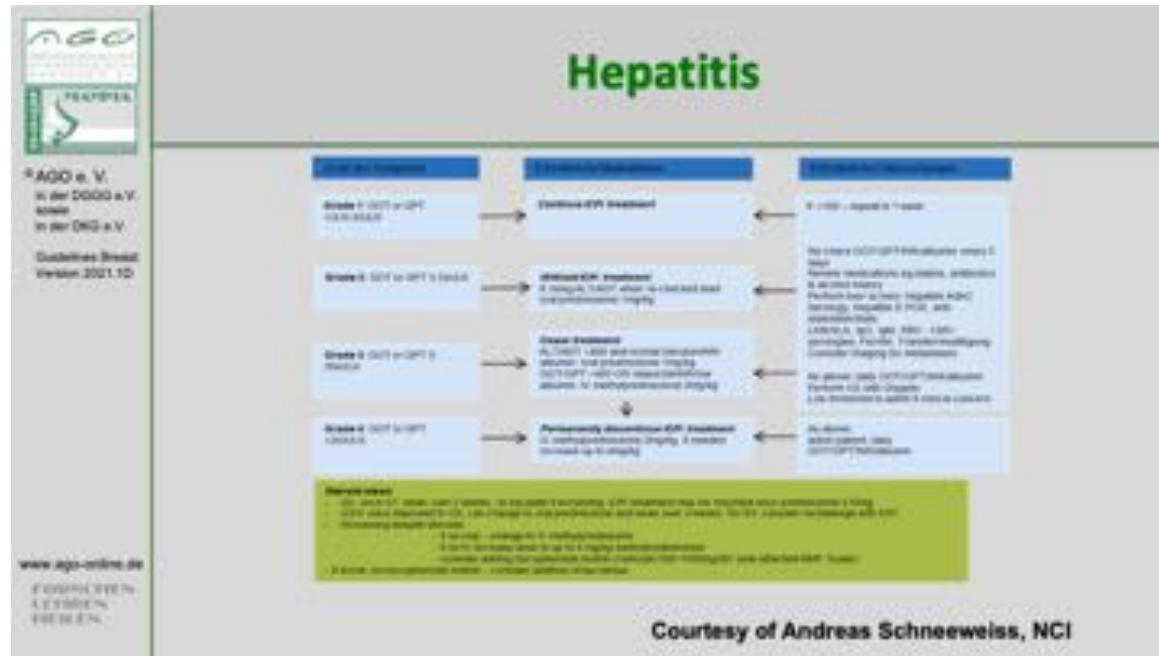
1. Haanen J, Carbonnel F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142.



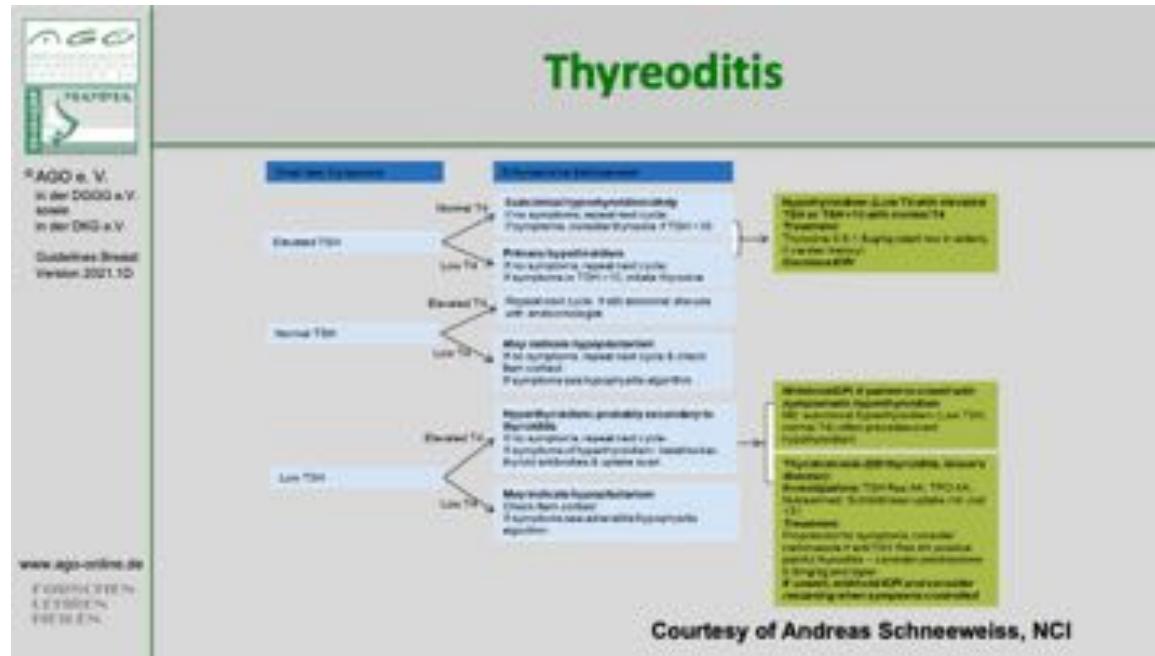
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1. Haanen J, Carbonnel F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142.



1. Haanen J, Carbonnel F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142.



1. Haanen J, Carbonnel F, Robert C, et al. on behalf of the ESMO Guidelines Committee: Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 119-142.



Nebenwirkungen nach Organsystemen Inzidenz, Prävention, Therapie

1. Infektionen

- Allgemeine Infektionsprophylaxe
- Hepatitis B-Screening
- Covid-19 (s. gemeinsame Stellungnahme mit DGHO)

www.ago-online.de
FORSCHEN
LEHREN
PRAESENZ



Allgemeine Infektionsprophylaxe

NB nur selten für solide Tumoren wie MaCa anwendbar
ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2018

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

* Definition Hochrisiko: vermutete Neutropenie dauer < 100/ μ l \geq 7d

ASCO:

Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, Langston AA, Nastoupil LJ, Rajotte M, Rolston K, Strasfeld L, Flowers CR: Outpatient management of fever and neutropenia in adults treated for malignancy: American society of clinical oncology and infectious diseases society of america clinical practice guideline update. J Clin Oncol 2018;36:1443-1453.

NCCN:

NCCN Guidelines Version 1.2020 Prevention and Treatment of Cancer-Related Infections.

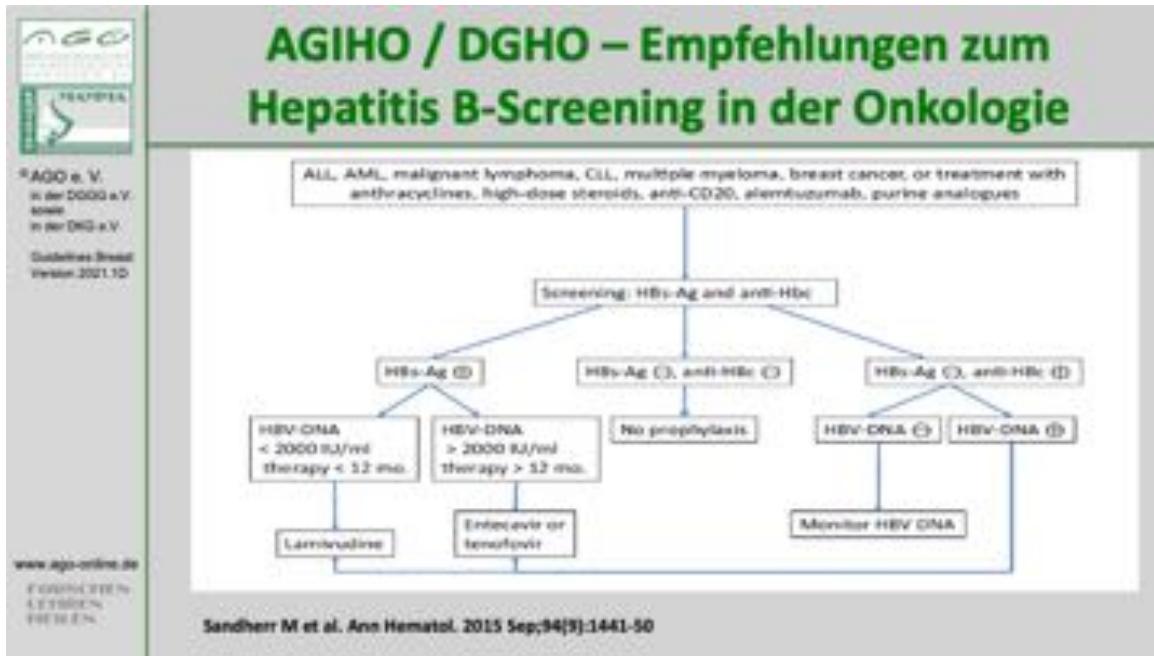
https://www.nccn.org/professionals/physician_gls/PDF/infections.pdf



Hepatitis B-Screening vor Chemotherapie

	Oxford		
	LoE	GR	AGO
• Hepatitis B-Screening vor Beginn einer Chemotherapie (HBsAG, anti-HBC)	2c	B	+
Bei Reaktivierung bzw. bei positiver Serologie			
• Unterbrechung der Chemotherapie	5	D	++
• Prophylaktische Therapie mit Virustatika bei Nachweis von HBV-DNA (entsprechend AGIHO/DGHO – Empfehlungen)	1b	A	++
• Hepatitis C-Screening vor Beginn einer Chemotherapie	5	D	+/-

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https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf



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Nebenwirkungen nach Organsystemen Inzidenz, Prävention, Therapie

2. Gutartige, bösartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)



Sekundäre Malignome I

		Oxford
	Löf	GR
• Die Induktion von soliden, malignen Tumoren durch Chemotherapie ist selten		2a
• Alkylantien erhöhen dosisabhängig das Risiko für Leukämien auf 0,2–0,4 % innerhalb von 10–15 Jahren		2a
• Anthrazyklinhaltige Regime erhöhen das Risiko für MDS und Leukämie auf 0,2–1,7 % innerhalb von 8–10 Jahren		2a
• PARP-Inhibitoren sind assoziiert mit einem erhöhten Risiko für AML und MDS von 0,5–1%		2b
• Radiotherapie erhöht das Risiko einer Leukämie bei Pat. mit einer anthrazyklinhaltigen Therapie um 0,2–0,4 %		2b
• Tamoxifen verdoppelt das Risiko für die Entwicklung eines Endometriumkarzinoms (bei Therapiebeginn ab 55. Lj.)		2b

Statements 1-4

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Tamoxifen and endometrial cancer

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet.* 2011 Aug 27;378(9793):771-84.
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Sekundäre Malignome II (nach Radiotherapie)

Oxford

LoE

1a

- Eine Radiotherapie (PMRT, BET) kann das Risiko für ein ipsilaterales Lungenkarzinom und Angiosarkom mäßiggradig anheben (10–15/10.000)
(Auftreten 5–10 Jahre nach PMRT)
 - Erhöhtes Risiko besonders für Raucher
 - Kein Unterschied bezgl. sekundärer Malignome zwischen PBI (Teil-) und WBI (Ganzbrustbestrahlung)

2b

2c

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Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

3. Erkrankungen des Blutes und des Lymphsystems

- Anämie
- Neutropenie
- Febrile Neutropenie



Anämie – Indikationen für den Einsatz von Erythropoese-stimulierenden Faktoren (ESF)

- Indiziert bei asymptomatischer Anämie
- Therapie und sekundäre Prophylaxe bei CTx-induzierter Anämie
 - Adjuvante Situation
 - Neoadjuvante/metastasierte Situation
 - Bei dosisdichter/dosenintakter CTx (ddCTC)
- Therapie beginnt bei Hb-Werten < 10g/dl
- Ziel-Hb 11–12 g/dL
- Verbesserung der Prognose (krankheitsfreies Intervall, Gesamtüberleben)
- ESF erhöht das Risiko von thromboembolischen Komplikationen

Oxford		
LoE	GR	AGO
Ia	B	+
Ia	A	+
Ia	A	+
Ia	A	±
Ib	A	+
Ia	A	+
Ia	A	+
Ia	B	-
Ia	A	

Leitlinie:

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020,

AWMF Registernummer: 032/054OL

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Relevante Leitlinien

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5. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.1, 2017, AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff 29. Januar 2018)



Praktischer Umgang mit ESF

- Epoetin α und Darbepoetin sind äquieffektiv
- Dosierungen:
 - Epoetin α: 150 IU/kg 3 x wöchentlich s.c. oder
40.000 IU 1 x / Woche s.c. oder
80.000 IU alle 2 Wochen s.c. oder
120.000 IU alle 3 Wochen s.c.
 - Epoetin β: 30.000 IE 1x / Woche s.c.
 - Darbepoetin: 2,25 µg/kg s.c. wöchentlich oder
500 µg s.c. alle 3 Wochen
- Hb-Messungen wöchentlich
 - Dosisreduktion bei Hb-Anstieg > 1 g/dl innerhalb von 2 Wo.
 - Dosissteigerung bei Hb-Anstieg < 1 g/dl innerhalb von 4–6 Wo.
- Bei FED ("funktioneller Eisenmangel") Eisensubstitution präferentiell i.v.
- Abbruch der ESF-Gabe bei ausbleibenden Hb-Anstieg nach 9 Wo.

1. Bohlius J, Bohlke K, Castelli R et al.: Management of cancer-associated anemia with erythropoiesis-stimulating agents: Asco/ash clinical practice guideline update. *J Clin Oncol* 2019;37:1336-1351.
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Relevante Leitlinien

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2. Rodgers GM, Gilreath JA et al: Cancer- and chemotherapy-induced anemia. NCCN Clinical Practice Guidelines in Oncology 2.2015. Available from: URL: <http://www.nccn.org>
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5. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020, AWMF Registernummer: 032/054OL



Granulozyten-Kolonie-stimulierende Faktoren

	Oxford		
	LoE	GR	AGO
• Primäre Prophylaxe für eine zu erwartende febrile Neutropenie (FN)			
• Bei Risiko für FN 10–20 %	1b	B	+/-
• Im Falle zusätzlicher individueller Risiken	1b	C	+
• Bei FN-Risiko > 20 % (z.B. DAC, dossidichte CT)	1a	A	++
• Sekundäre Prophylaxe während der Chemotherapie (frühere FN oder Neutropenie Grad IV > 7 Tage)	1b	A	++
• Therapeutischer Nutzen bei FN	1a	A	+/-
• Beginn der Therapie in Verbindung mit Art und Dauer der Chemotherapie			
• Pegfilgrastim Tag 2	1b	A	++
• Lipegfilgrastim Tag 2	1b	A	++
• Filgrastim/Lenograstim von Tag 2–5 bis absolute Neutrophilenzahl > 2–3 × 10 ⁹	1b	A	++

Relevante Leitlinien

1. S3-Leitlinie: Supportive Therapie:

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3 – Februar 2020

2. NCCN Guidelines 2020

3. Smith TJ, Bohlke K, Lyman GH, et al.: American Society of Clinical Oncology. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015 Oct 1;33(28):3199-212.

Statements 1-4

- Bondarenko I, Gladkov OA, Elsaesser R et al.: Efficacy and safety of lipegfilgrastim versus pegfilgrastim: a randomized, multicenter, active-control phase 3 trial in patients with breast cancer receiving doxorubicin/docetaxel chemotherapy. BMC Cancer 2013, 13:386.
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- Loibl S, Mueller V, von Minckwitz G et al.: Comparison of pegfilgrastim on day 2 vs. day 4 as primary prophylaxis of intense dose-dense chemotherapy in patients with node-positive primary breast cancer within the prospective, multi-center GAIN study: (GBG

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Management der febrilen Neutropenie

Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO)
 der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de

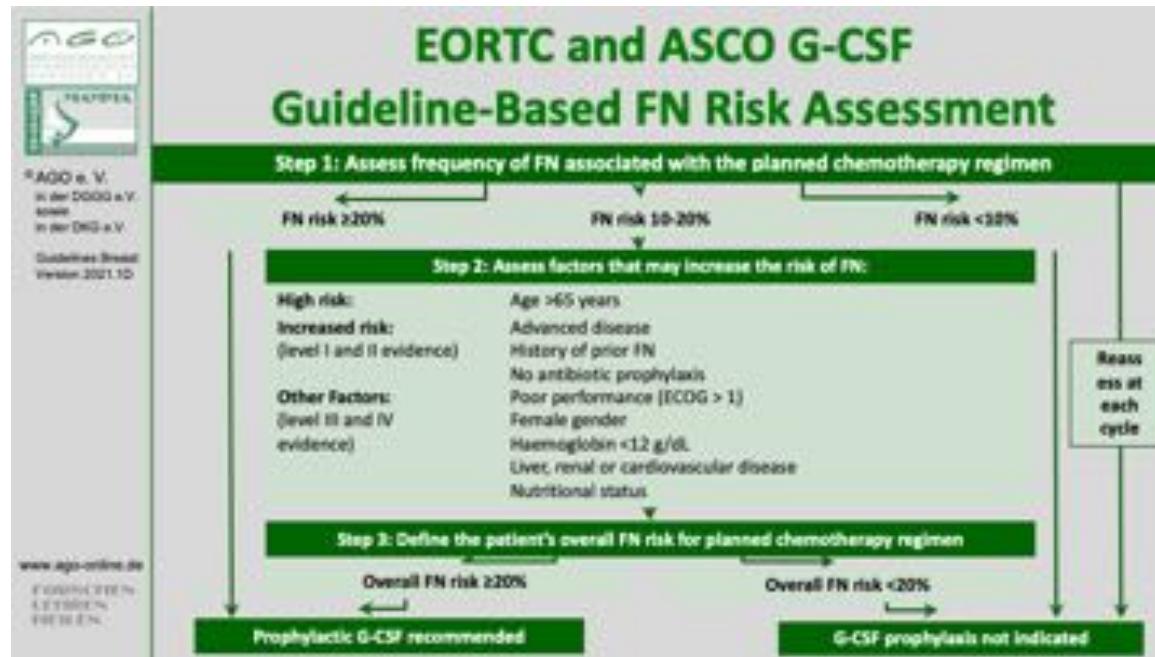
Definition (orale Temp. > 38,5°C oder zwei konsekutive Messungen > 38°C über 2 h in einer Patientin mit einem ANC < 500 cells/mm³ oder erwarteter Abfall < 500 cells/mm³)

Oxford

	LoE	GR	AGO
• Klinische Untersuchung	5	D	++
• Tägliche Kontrollen	5	D	++
• Hospitalisierung von Hochrisikopatienten	1b	A	++
• Ambulante Therapie bei Niedigrisikopat. möglich	1b	A	+
• Differentialblutbild	5	D	++
• Blutkulturen	5	D	++
• Bildgebung der Lunge	3	C	++
• Sofortige empirische antibiot. Therapie	1a	A	++
• Empirische antimykotische Therapie nach 4–7d bei keiner Besserung unter der antibiotischen Therapie	1b	A	++
• G-CSF als therapeutische Maßnahme	2b	B	+/-

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4. Nebenwirkungen am Ovar

Therapie-assoziierte Amenorrhoe (CRA, CIA, TIA)	Oxford LoE
• Eine CRA kann dauerhaft oder vorübergehend sein (abhängig vom Alter der Pat. und der Art der Chemotherapie)	2b
• Das Risiko der CRA steigt mit dem Alter / Therapiedauer	2b
• CRA ist ein (unsicherer) Surrogatmarker für Menopause und Fertilität	5
• Eine adjuvante endokrine Therapie mit einem GnRHa induziert eine reversible Amenorrhoe, und verschiebt eine Konzeption in eine weniger fertile Phase	5
• Die Ovarialreserve der nach Chemotherapie prämenopausal gebliebenen Frauen ist reduziert	2b
• CRA ist mit einer verbesserten Prognose (DFS/OS) assoziiert	1b

Synonyma: Chemotherapie / Therapie-induzierte Amenorrhoe (TIA/CIA)

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Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

5. Psychiatrische Erkrankungen

- Depression
- Fatigue
- Kognitive Störungen
- Schlafstörungen



(Therapie assoziierte) Depression

	Oxford		
	LoE	GR	AGO
• Depressive Episoden bei 20–30% der Mammakarzinompatientinnen	2a	B	
• Psychosoziale Interventionen verbessern Depression, allerdings ohne günstige Auswirkungen auf Mortalität	1b	A	
• Antidepressiva können Depression bei Brustkrebspatientinnen verbessern	1b	A	
• Körperliches Training kann Depression bei Brustkrebspatientinnen verhindern	2b	B	+

Statements 1-4

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(Therapie-assozierte) Fatigue

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

- Fatigue häufiges Symptom bei Brustkrebspatientinnen (30–60%)
- Ausschluss anderer Ursachen (Anämie, Tumorausdehnung, Begleiterkrankungen, Medikamente) für Fatigue
- Gezielte psychosoziale Interventionen können Fatigue lindern
- Körperliches Training kann Fatigue verbessern
- Diät, Yoga können Fatigue verbessern
- Methylphenidate kann Fatigue verbessern

Fatigue is frequently present...

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Physical exercise.....

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Methylphenidate...

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(Therapie-assoziierte) Kognitive Störungen

	Oxford	
	LoE	GR
• Therapiebedingte kognitive Störungen (sog. „Chemobrain“) häufig beschrieben (16–75%)	2a	B
• Verhaltenstherapie kann kognitive Funktion verbessern	2b	B
• Methylphenidate kann kognitive Funktion bei Patientinnen mit Krebs verbessern	3a	C
• Unter Aromatasehemmertherapie wurden kognitive Störungen beobachtet (insbes. Wortgedächtnis)	1a	B

Therapiebedingte kognitive Störungen (sog. „Chemobrain“) häufig beschrieben

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(Therapie-assozierte) Schlafstörungen

Oxford
LoE GR AGO
2a B

1b A ++

- Schlafstörungen häufig bei Mammakarzinom-patientinnen während und nach Therapie beschrieben (20–70%)
- Verhaltenstherapie ist effektiv in der Behandlung von Schlafstörungen und Steigerung der Lebensqualität

Sleep disturbances are a common problem....

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Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

6. Erkrankungen des Nervensystems

- Chemotherapie induzierte periphere Neuropathie (CIPN)



Chemotherapie-induzierte periphere Neuropathie (CIPN)

- Inzidenz Grad 1–2 nach Taxanen 20–50 %
- Inzidenz Grad 3–4 nach Taxanen 6–20 %
- Risikofaktoren: Art der Chemotherapie, Dosierung, BMI, fehlende körperliche Aktivität
- Individuelle Risikofaktoren
 - + Diabetes mellitus
 - + Nutritiv-toxische Substanzen ins. Alkohol
 - + Niereninsuffizienz
 - + Hypothyreose
 - + Kollagenosen / Vaskulitiden
 - + Vitaminmangel
 - + HIV-Infektion
 - + CMT-Genmutation
- Unklar:
 - + Andere genetische Faktoren (SNP, Mutationen)

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Supportive Therapie bei onkologischen PatientInnen - Langversion 1.1, 2017, AWMF Registernummer: 032/054OL,
<http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff 29. Januar 2018)



Chemotherapie-induzierte periphere Neuropathie – Prävention –

	Oxford		
	LoE	GR	AGO
Nicht-medikamentöse Prävention			
• Funktionstraining (Fitness, sensomotorisches Stimulationstraining etc.)	S	D	+
• Kompressionstherapie (chirurgische Handschuhe, Kompressionsstrümpfe)	2b	B	+
• Kühlhandschuhe und Kühlstrümpfe	2b ¹	B	+
• Elektro-Akupunktur	1b	B	-
Medikamentöse Prävention			
Es besteht keine wirksame medikamentöse Prophylaxe der CIPN			
• Venlafaxin	2a	C	+/-
• Palmitoylethanolamid (PEA) topisch oder p.o.	S	D	+/-
• Alpha-Liponsäure, Amifostin, Amitriptylin, Acetyl-L-Carnitin, Carbamazepin, Elektrolytlösungen, Glutathion, Goshajinkigan (GIG), Ocarbazepin, Vitamin B, Vitamin E oder andere Substanzen ²	1b	A	-

¹ Unter nicht empfohlener Medikamente bei Hershman et al. 2014

Reviews/Leitlinien

1. Hershman DL, Lacchetti C, Dworkin RH, et al.: American Society of Clinical Oncology. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jun;20(32):1941-67.
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Nicht-medikamentöse Prävention

Funktionstraining

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Kompression

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Kühlung

1. Hanai A, Ishiguro H, Sozu T et al. (2016) The effects of frozen gloves and socks on paclitaxel-induced peripheral neuropathy among patients with breast cancer: A selfcontrolled clinical trial. J Clin Oncol 34(suppl): (abstr 10022). <http://meetinglibrary.asco.org/content/166655-176>.
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Elektro-Akupunktur

1. Greenlee H, Crew KD, Capodice J, et al.: Randomized sham-controlled pilot trial of weekly electro-acupuncture for the prevention of taxane-induced peripheral neuropathy in women with early stage breast cancer. *Breast Cancer Res Treat.* 2016 Apr;156(3):453-464.

Medikamentöse Prävention

Venlafaxin

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Palmitoylethanolamid (PEA)

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Verschiedene Substanzen

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Acetyl-L-Carnitin

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Chemotherapie-induzierte periphere Neuropathie – Therapie –

	Oxford		
	LoE	GR	AGO
Nicht-medikamentöse Therapie			
▪ Funktionstraining (Fitness, sensomotorisches Stimulationstraining etc.)	2a	C	+
▪ Physiotherapie / physikalische Therapie	5	D	+
▪ Akupunktur	2b	B	+
Medikamentöse Therapie			
▪ Menthol lokal (1%), Capsaicin/Lidocain lokal	5	D	+
▪ Baclofen/Amitriptylin/Ketamin-Creme	2b	B	+
▪ Duloxetin zur Behandlung von Schmerzen durch CIPN	1b	B	+
▪ Opioide zur Behandlung von Schmerzen durch CIPN	5	D	+
▪ Palmitoylethanolamid (PEA) topisch oder p.o.	5	D	+/-
▪ Venlafaxin	5	D	+/-
▪ Gabapentin, Pregabalin	1b	B	+/-
▪ Amitriptylin/ Nortriptylin, Imipramin/Desipramin	1b	B	+/-
▪ Acetyl-L-Carnitin, Lamotrigin oder andere Substanzen ¹	1b	B	-

¹ Liste nicht empfohlener Medikamente bei Hershman et al. 2014

Reviews / Leitlinien

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Nicht-medikamentöse Therapie

Funktionstraining

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Medikamentöse Therapie

Menthol / Capsaicin

1. Fallon MT, Storey DJ, Krishan A, et al.: Cancer treatment-related neuropathic pain: proof of concept study with menthol--a TRPM8 agonist. Support Care Cancer. 2015 Sep;23(9):2769-77
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Baclofen/Amitriptylin/Ketamin-Creme

1. Barton DL, Wos EJ, Qin R, et al.: A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Support Care Cancer*. 2011 Jun;19(6):833-41.
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Duloxetin

1. Smith EM, Pang H, Cirrincione C, et al.: Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA*. 2013 Apr 3;309(13):1359-67

Akupunktur:

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Gabapentin, Pregabalin:

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Nebenwirkungen nach Organsystemen Inzidenz, Prävention, Therapie

7. Herzerkrankungen



**Langzeittoxizität
Kardiotoxizität**

	Oxford	LoE	GR	AG
• Äquivalente Kardiotoxizität von Doxorubicin und Epirubicin in den empfohlenen Dosierungen (450-500 bzw. 900-1000 mg/m ² kum. Dosis)		2b	B	
• Weniger Kardiotoxizität nach liposomalem Doxorubicin		1b	B	
• Risikofaktoren für Anthrazyklin- oder Trastuzumab-assoziierte Kardiotoxizität		2b	B	
◦ Alter, Übergewicht, Hypertonus, Hypercholesterinämie, vorbestehende Herzerkrankungen (inkl. grenzwertige LVEF), Diabetes mellitus				

Statements

“Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)”

“Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity”

1. van Dalen EC. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. Cochrane Database Syst Rev. 2010 Mar 17;(3):CD005006. Review. Update in: Cochrane Database Syst Rev. 2010;(5):CD005006.

"Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently..."

1. Petrelli F: Mortality, leukemic risk, and cardiovascular toxicity of adjuvant anthracycline and taxane chemotherapy in breast cancer: a meta-analysis. *Breast Cancer Res Treat.* 2012 Sep;135(2):335-46
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“Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors.”

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 2. de Azambuja E, Ponde N, Procter M, et al: A pooled analysis of the cardiac events in the trastuzumab adjuvant trials. Breast Cancer

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3. Kabore EG, Guenancia C, Vaz-Luis I, et al: Association of body mass index and cardiotoxicity related to anthracyclines and trastuzumab in early breast cancer: French canto cohort study. PLoS medicine 2019;16:e1002989.
4. Leemasawat K, Phrommintikul A, Chattipakorn SC, Chattipakorn N: Mechanisms and potential interventions associated with the cardiotoxicity of erbB2-targeted drugs: Insights from in vitro, in vivo, and clinical studies in breast cancer patients. Cell Mol Life Sci 2019.
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“Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)”

1. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments: what the cardiologist needs to know. Nat Rev Cardiol. 2010 Oct;7(10):564-75. Review.
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Troponin as Early Predictor for Cardiotoxicity

- 1. Ponde N, Bradbury I, Lambertini M, et al. Cardiac biomarkers for early detection and prediction of trastuzumab and/or lapatinib-induced cardiotoxicity in patients with HER2-positive early-stage breast cancer: a NeoALTTO sub-study (BIG 1-06). *Breast Cancer Res Treat*. 2017 Dec 27.
- 2. Kitayama H, Kondo T, Sugiyama J, et al.: High-sensitive troponin T assay can predict anthracycline- and trastuzumab-induced cardiotoxicity in breast cancer patients. *Breast Cancer*. 2017 Nov;24(6):774-782.

Betablocker-Prophylaxe

- 1. Gujral DM, Lloyd G, Bhattacharyya S. Effect of prophylactic betablocker or ACE inhibitor on cardiac dysfunction & heart failure during anthracycline chemotherapy ± trastuzumab. *Breast*. 2018 Feb;37:64-71.
- 2. Oliva S, Cioffi G, Frattini S, et al.: Administration of angiotensin-converting enzyme inhibitors and β-blockers during adjuvant trastuzumab chemotherapy for nonmetastatic breast cancer: marker of risk or cardioprotection in the real world? *Oncologist*. 2012;17(7):917-24.
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Trastuzumab Adjuvant Überwachung hinsichtlich CHF

Oxford LoE: 5

GR: D

AGO: ++

Vor Beginn der Trastuzumab-Therapie

- Anamnese, klinische Untersuchung (Ödeme, Hepatomegalie)
- Echokardiographie (Alternative zu MUGA)

} Bestimmung der LVEF

Während und nach der Trastuzumab-Therapie

Regelmäßige Dokumentation von

- Herzfrequenz; bei Anstieg > 15 % über das individuelle Ausgangsniveau
- Körpergewicht; bei Anstieg ≥ 2 kg/Woche
- Kardiale Zeichen und Symptome

LVEF alle 3 Monate

Statement: Cardiac Monitoring (5 D++)

Vote result of the AGO recommendation: 100%

1. Perez EA, Suman VJ, Davidson NE, et al.: Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol.* 2008 Mar 10;26(8):1231-8. Epub 2008 Feb 4.
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Toxizitätssteigerungen durch Behandlungskombinationen

Oxford

LoE GR AGO

Kardiale Toxizität

- Trastuzumab simultan zur Radiotherapie
- Trastuzumab simultan zu Epirubicin
- Trastuzumab simultan zu Doxorubicin
- Anthrazykline simultan zur Radiotherapie

2b B +

2b B +/-

2b B -

2c C -

Risiko Lungen- / Brustparenchymfibrosen

- Tamoxifen simultan zu Radiotherapie
- Chemotherapie simultan zu Radiotherapie

3 C +/-

1b B -

"Trastuzumab simultaneous to radiotherapy"

1. Halyard MY, Pisansky TM, Dueck AC: Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG Phase III Trial N9831. *J Clin Oncol* 27: 2638-2644, 2009
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3. Kroeze SG, Fritz C, Hoyer M, et al.: Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review. *Cancer Treat Rev*. 2016 Dec 19;53:25-37. doi: 10.1016/j.ctrv.2016.11.013. [Epub ahead of print]

"Trastuzumab simultaneous to epirubicin"

1. Untch M, Muscholl M, Tjulandin S, et al.: First-line trastuzumab plus epirubicin and cyclophosphamide therapy in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: cardiac safety and efficacy data from the Herceptin, Cyclophosphamide, and Epirubicin (HERCULES) trial. *J Clin Oncol*. 2010 Mar 20;28(9):1473-80.
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Breast. 2016 Oct;29:153-9. doi: 10.1016/j.breast.2016.07.017. Epub 2016 Aug 5.

"Trastuzumab simultaneous to doxorubicin"

1. Slamon D, Eiermann W, Robert N, et al.: Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med.* 2011 Oct 6;365(14):1273-83

"Anthracycline simultaneous to radiotherapy"

1. Toledano A, Garaud P, Serin D, et al.: Concurrent administration of adjuvant chemotherapy and radiotherapy after breast-conserving surgery enhances late toxicities: long-term results of the ARCOSEIN multicenter randomized study. *Int J Radiation Oncology Biol. Phys.* 2006; 65: 324-332.

"Tamoxifen simultaneous to radiotherapy"

1. Kraus-Tiefenbacher U, Sfintizky A, Welzel G, et al.: Factors of influence on acute skin toxicity of breast cancer patients treated with standard external beam radiotherapy (EBRT) after breast conserving surgery (BCS). *Radiat Oncol.* 2012 Dec 18;7(1):217. [Epub ahead of print]
2. Varga Z, Cserháti A, Kelemen G, et al.: Role of systemic therapy in the development of lung sequelae after conformal radiotherapy in breast cancer patients. *Int J Radiat Oncol Biol Phys.* 2011 Jul 15;80(4):1109-16.
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1. Valakh V, Trombetta MG, Werts ED, et al.: Influence of concurrent anastrozole on acute and late side effects of whole breast radiotherapy. *Am J Clin Oncol.* 2011 Jun;34(3):245-8.
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- Swain SM, Ewer MS, Cortés J, et al.: Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. *Oncologist.* 2013;18(3):257-64. doi: 10.1634/theoncologist.2012-0448. Epub 2013 Mar 8.



Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

8. Erkrankungen des Gastrointestinaltrakts

- Nausea, Emesis (Übelkeit, Erbrechen)
- Mukositis
 - Stomatitis (Everolimus)
- Diarrhoe
- Obstipation



Antiemetische Therapie nach MASCC und ASCO

	Oxford		
	LoE	GR	AGO
• Abschätzen des emetogenen Potenzials des jeweiligen Chemotherapie-Protokolls	5	D	++
• Neurokinin-1-Rezeptor-Antagonisten	1b	A	++
• Dexamethason (auch bei Kombinationen mit ICPI)	1a	A	++
• 5-HT ₃ -Antagonisten	1b	A	++
• Feste Kombination mehrerer Substanzen	1b	A	++
• Reserveantimetika (Rescue Medication)			
• Olanzapin	1b	A	+
• Levomepromazin, Benzodiazepine	3b	C	+
• Cannabinolide, Ingwer	3b	C	+

ICPI=immuncheckpointinhibitor

1. Hesketh, Paul J, Kris MG, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2017;35(28):3240-61
2. Walsh D, Davis M, Ripamonti C, et al.: 2016 updated mascc/esmo consensus recommendations: Management of nausea and vomiting in advanced cancer. *Support Care Cancer* 2017;25:333-340.
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 - 14. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al.: Aprepitant Protocol 054 Study Group. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer*. 2003 Jun 15;97(12):3090-8.
 - 15. Massa E, Astara G, Madeddu C, et al.: Palonosetron plus dexamethasone effectively prevents acute and delayed chemotherapy-induced nausea and vomiting following highly or moderately emetogenic chemotherapy in pre-treated patients who have failed to respond to a previous antiemetic treatment: Comparison between elderly and non-elderly patient response. *Crit Rev Oncol Hematol*. 2008 Aug 23. [Epub ahead of print]
 - 16. Grunberg SM, Dugan M, Muss H, et al.: Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy. *Support Care Cancer*. 2008 Nov 27. [Epub ahead of print]
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 - 19. Olver I, Paska W, Depierre A, et al.: A multicentre, double-blind study comparing placebo, ondansetron and ondansetron plus dexamethasone for the control of cisplatin-induced delayed emesis. *Ondansetron Delayed Emesis Study Group*. *Ann Oncol*. 1996

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21. Paul J. Hesketh, Mark G. Kris, Ethan Basch et al.: (Antiemetics: ASCO Guideline Update 2020) Journal of Clinical Oncology 2020 38:24, 2782-2797

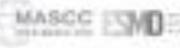
Olanzapine

- 1 Hironobu H, Masakazu A, Osamu Tokuyama, et al. Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial Lancet Oncology December 11, 2019 DOI: [https://doi.org/10.1016/S1470-2045\(19\)30678-3](https://doi.org/10.1016/S1470-2045(19)30678-3)
- 2 Slimano F, Netzer F, Borget I et al.: Olanzapine as antiemetic drug in oncology: a retrospective study in non-responders to standard antiemetic therapy. Int J Clin Pharm. 2018 Oct;40(5):1265-1271. doi: 10.1007/s11096-018-0649-1. Epub 2018 May 9.
- 3 Hashimoto H, Abe M, Tokuyama O, et al.: Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (j-force): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019.


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

EMETIC RISK GROUP	ANTIEMETICS				
High Non-AC	S-HT ₂	+	DEX	+	5-HT ₃
High AC	S-HT ₂	+	DEX	+	5-HT ₃
Carboplatin	S-HT ₂	+	DEX	+	5-HT ₃
Moderate (lower than carboplatin)	S-HT ₂	+	DEX		
Low	S-HT ₂	OR	DEX	OR	DOP
Minimal	No routine prophylaxis				
S-HT ₂ -receptor antagonists (eg metoclopramide)		5-HT ₃ -receptor antagonists (eg ondansetron)		5-HT ₂ -receptor antagonists (eg ciproheptadine) and/or DOP-agonists (eg apomorphine) and/or benzodiazepines	
<small>NOTE: Intra-HC receptor antagonists are not available for antiemetic therapy, particularly for the prevention of 5-HT₃-receptor antagonists (e.g. Ondansetron may be used particularly if nausea is a concern).</small>					
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Antiemetische Therapie

DELAYED Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	DEX → d. APR 125mg für adulte
High AC	NONE → d. APR 125mg für adulte
Cancer	NONE → d. APR 125mg für adulte
Dexametazan, or anticholinergics, or metoclopramid	DEX can be considered
Moderate (adult)	No routine prophylaxis
Low and Minimal	No routine prophylaxis
DEX = Dexamethason MCP = METOCLOPRAMID APR = APERIPTANT ISLZ = CLARASOPHATE	

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

Supportive Therapie

Antiemetika

Molekülgruppe	Substanz	Dosierung	Weiterentwicklungen	Potenzial
Serotonin-antagonisten	Ondansetron Tropisetron Ondasetron Palonsetron	0 mg i.v., 2-40 mg p.o. 0 mg i.v., 3 mg i.m. 0-4 mg i.v. 0,25 mg p.o.	Kopfschmerzen, Narcolese, Hochdruckprophylaxe Transtuzumabemabtag Combinations in hoher Dosierung	sehr hoch
5-HT3-Antagonisten	Aprepitant Fosaprepitant Rompitant	125 mg i.v. 30 mg d 1-2 p.o. 125 mg i.v./d. 160 mg d 1 p.o.	Cyberonine P-450-Mindestmenge mit Dosis-reduktion nach Ondansetron (2-8 mg). Keine Kombination mit Atemosenz. Tropisetron, Ondasetron	sehr hoch
Dopamin-antagonisten/ anticholinergische Antagonisten	Melatonin Alizapride	bis zu 120 mg/24h als Gastroresinat ed. als Trocken- pulpa (200 mg i.v. oder p.o./24h) 0,5 Amp. ed. 8 Tbl.)	Syndrome (Antikid. Epizoden)	hoch
Dopamine	Ondansetron	250mg/d für d1-4 80g/100g/d für d5-9	Sedation, Bewegungsaufnahme	hoch
Phenothiazine/ Butyrophenone	Haloperidol	0,2 mg d 4-5/d	Sedation, Verkürzung der Akkordienzeitweile, Immobilität, Lebenserwartung	mäßig
Antihistaminide	Dexamethason Prednisolon	0,05-0,05 mg i.v., 1-5 mg/d	Muskelerschlaffung, psychotische Reaktionen, Rauch, Blutdrucksenkung	mäßig
Benzodiazepine	Diazepam Lorazepam	bis zu 20 mg/d 0,5-1,0 mg/d	Sedation, Antikonvulsant	gering
5-HT3 (Antagonist) und Palonsetron	Über-Kombinations- partner (neut)	ab 300 mg Pd 0,3 mg		sehr hoch

Olanzapine

1. Hironobu H, Masakazu A, Osamu Tokuyama, et al. Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial Lancet Oncology December 11, 2019 DOI:[https://doi.org/10.1016/S1470-2045\(19\)30678-3](https://doi.org/10.1016/S1470-2045(19)30678-3)
2. Slimano F, Netzer F, Borget I et al. Olanzapine as antiemetic drug in oncology: a retrospective study in non-responders to standard antiemetic therapy. Int J Clin Pharm 2018 Oct;40(5):1265-1271. doi: 10.1007/s11096-018-0649-1. Epub 2018 May 9.
3. Hashimoto H, Abe M, Tokuyama O, et al: Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (j-force): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019.

Mukositis Prävention

[http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006\(dTV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006(dTV).pdf)
 Multidisciplinary S3 guidelines of the AWMF (Reg.-Nr. 032-054OL): „Supportive Therapie bei onkologischen Patientinnen – interdisziplinäre Querschnittsleitlinie“, released 21.11.2016

Oxford	LeE	GR	AGO
2b	++		

- + Standardisierte Mundpflege zur Prophylaxe oraler Mukositis soll in allen Altersgruppen und bei allen Krebsbehandlungen mit einem Risiko für OM erfolgen

Diese besteht aus:

1. Patientinnenviertig
 - regelmäßige Mundspülung (H₂O, NaCl)
 - Weiche Zahnbürste
 - Reinigung der Zahzwischenräume mit Zahnsaide und/oder Interdentalbürsten
 - Vermeidung von Nüssen (Alkohol, Tabak, scharfe Speisen, säurehaltige Lebensmittel)
 - Fortlaufende Kontrolle auf Läsionen
2. Risikoadaptierte vorbeugende Maßnahmen durch den Zahnarzt
3. Engmaschige Klinische Kontrolle

Keine Evidenz besteht für folgende Substanzen: Alokapurinol, Capsaicin, Glutamin, Honig, Kamille, Kamillosen, Kaugummi, Kefir, Methodon, Nystatin, Pentoxifyllin, Polividon Jod, Vitamine A/U/Kombinationen

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

1. RV Lalla, J Bowen, RV Lalla, et al.: MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 2014; 120:1453-61
2. McGuire DB, Fulton JS, Park J, et al.: Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients. *Support Care Cancer* 2013 Nov;21(11):3165-77.
3. Jensen, S. B., V. Jarvis, Y. Zadik, et al.: "Systematic review of miscellaneous agents for the management of oral mucositis in cancer patients." *Support Care Cancer* 2013;21(11): 3223-3232.
4. Leenstra, J. L., R. C. Miller, R. Qin et al.: "Doxepin rinse versus placebo in the treatment of acute oral mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy: a phase III, randomized, double-blind trial (NCCTG-N09C6 [Alliance]). *J Clin Oncol* 2014;32(15): 1571-1577.
5. Nicolatou-Galitis, O., T. Sarri, J. Bowen, et al.: Systematic review of amifostine for the management of oral mucositis in cancer

- patients. *Support Care Cancer* 2013; 21(1): 357-364.
- 7. Peterson, D. E., K. Ohrn, J. Bowen, et al.: Systematic review of oral cryotherapy for management of oral mucositis caused by cancer therapy. *Support Care Cancer* 2013; 21(1): 327-332.
 - 8. Saunders, D. P., J. B. Epstein, S. Elad, J, et al.: Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients. *Support Care Cancer* 2013; 21(11): 3191-3207.
 - 9. Yarom, N., A. Ariyawardana, A. Hovan, et al.: Systematic review of natural agents for the management of oral mucositis in cancer patients. *Support Care Cancer* 2013;21(11):3209-21.



Prophylaxe der Everolimus-bedingten Stomatitis durch Cortison-basierte Mundspülung

- Studiendesign: einarmige Phase II-Studie
- Kohorte: 92 Pat. behandelt mit Everolimus und Exemestane
- Schedule: 10 ml Dexamethason (15mg/5ml Lösung)
4 x täglich über 8-12 Wochen*
- Ergebnisse: all-grade Inzidenz der Stomatitis 27%
(13 Wochen Exposition) mit 9% >= Grad 2 Events

* alternativ Hydrocortison: Hydrocortisonacetat-Suspension 0,5 % mit Lidocainhydrochlorid und Dexpanthenol (Arzneibuchrezeptur NBF 7.14.)

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

1. Rugo HS, Seneviratne L, Beck JT, et al: Prevention of everolimus-related stomatitis in women with hormone receptor-positive, her2-negative metastatic breast cancer using dexamethasone mouthwash (swish): A single-arm, phase 2 trial. Lancet Oncol 2017;18:654-662.
2. Jones VE, McIntyre KJ, Paul D, Wilks ST, et al.:Evaluation of miracle mouthwash plus hydrocortisone versus prednisolone mouth rinses as prophylaxis for everolimus-associated stomatitis: A randomized phase ii study. Oncologist 2019;24:1153-1158.



Mukositis

[http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2020\(dtV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2020(dtV).pdf)

- Desinfizierende / entzündungshemmende Maßnahmen:
Mundspülung mit Kamille- oder Salbeitee bzw. Kamillenextrakt, äther. Öle, Iod-Polyvidon, Hexetidin, Pinselungen mit Kristallviolettlösung 0,5% (Rezeptur) oder Myrrhentinktur; H. Mometasonefuranat + Propylenglykol
- Schleimhautschützende Maßnahmen (während / nach Zytostatikapplikation):
Lutscheln von Eiswürfeln (bes. geeignet: Ananassaft, über die Apotheke beziehbar) während 5-Fluorouracil- oder HD-Melphalan-Infusion. Calciumfolinat (Leucovorin-Mundgut®, H) bei HD-Methotrexat: frühestens 24 Stunden nach Ende MTX-Infusion beginnen (sonst Wirkungsverlust des Zytostatikums!), 4- bis 6-stündig.
Dexpanthenol (Panthenol®-Lsg. 5%; H) mehrmals täglich zur Mundspülung
- Lokale antimykotische Therapie:
Amphotericin B, Nystatin, Fluconazol
- Lokale antivirale Therapie
Aminoquinurid / Tetracain-HCl, Aciclovir
- Lokalanästhetika:
Orale Anwendung von Benzocain, Doxepin 0,5 %
- Schmerztherapie: Opioide bei Bedarf

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

1. [http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006\(dtV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006(dtV).pdf)
2. RV Lalla, J Bowen RV Lalla, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 2014; 120:1453-61
3. McGuire DB, Fulton JS, Park J, et al; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients. *Support Care Cancer* 2013 Nov;21(11):3165-77.
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- patients. *Support Care Cancer* 2013; 21(1): 357-364.
- 7. Peterson, D. E., K. Ohrn, J. Bowen, et al.: Systematic review of oral cryotherapy for management of oral mucositis caused by cancer therapy. *Support Care Cancer* 2013; 21(1): 327-332.
 - 8. Saunders, D. P., J. B. Epstein, S. Elad, et al.: Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients. *Support Care Cancer* 2013; 21(11): 3191-3207.
 - 9. Yarom, N., A. Ariyawardana, A. Hovan, et al.: Systematic review of natural agents for the management of oral mucositis in cancer patients. *Support Care Cancer* 2013; 21(11): 3209-21.
 - 10. Elad S., Kin Fong Cheng K et al. MASCC/ISOO clinical practice Guidelines for the Management od Mucositis Secondary to Cancer Therapy *Cancer* 126: 4423-4431, 2020

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

1. D. E. Peterson, C. B. Boers-Doets, R. J. Bensadoun, et al. on behalf of the ESMO Guidelines Committee Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up Annals of Oncology 2015;26 (Supplement 5): v139–v151.
2. Stein A, Voigt W, Jordan K. Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management Ther Adv Med Oncol 2010;2(1) 51-63
3. Coyle, V. M., D. Lungulescu, C. Toganel, et al. (2013). "A randomised double-blind placebo-controlled phase II study of AGI004 for control of chemotherapy-induced diarrhoea." Br J Cancer 2013;108(5):1027-1033.
4. Hoff, P. M., D. F. Saragiotto, C. H. Barrios, et al. (2014). "Randomized Phase III Trial Exploring the Use of Long-Acting Release Octreotide in the Prevention of Chemotherapy-Induced Diarrhea in Patients With Colorectal Cancer: The LARCID Trial." J Clin Oncol 2014;32:1006-11
5. Kee, B. K., J. S. Morris, R. S. Slack, et al. "A phase II, randomized, double blind trial of calcium aluminosilicate clay versus placebo for the prevention of diarrhea in patients with metastatic colorectal cancer

- treated with irinotecan." *Support Care Cancer* 2015;23:661-70.
7. Middleton, G., S. Brown, C. Lowe, T. et al. (2013). "A randomised phase III trial of the pharmacokinetic biomodulation of irinotecan using oral ciclosporin in advanced colorectal cancer: results of the Panitumumab, Irinotecan & Ciclosporin in COLOrectal cancer therapy trial (PICCOLO)." *Eur J Cancer* 2013, 49(16): 3507-3516.



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Obstipation

Wichtige Nebenwirkung einer Opiattherapie

- **Quellmittel**
 - Flachsamen, Leinsamen (geschrotet)
- **Osmotisch wirksame Laxanzien**
 - Macrogol > Lactulose (Cochrane Review **LoE 1a AGO +**)
 - Orale Kontrastmittel; Ultima ratio z.B. Natriumamidotrizoat
 - Sorbit
- **Stimulierende Laxanzien**
 - Sennesfrüchte, Rizinusöl, Bisacodyl, Natriumpicosulfat
- **Stuhlweichmacher**
 - Gleitmittel z.B. Paraffin
- **Opiod-Rezeptorantagonist bei Opiatobstipation**
 - Methylnaltrexone

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)



Nebenwirkungen nach Organsystemen Inzidenz, Prävention, Therapie

9. Erkrankungen der Haut und des Unterhautgewebes

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,
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Hauttoxizität

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

• Vermeidung einer ausgeprägten chemotherapie-induzierten Alopezie durch Kopfhautkühlung*

• Eine Prophylaxe des HFS mit harnstoffhaltigen 5–10% Cremes kann erfolgen (mehrfach tägl.)

• Unter Docetaxel sollte eine Prophylaxe der Nagelveränderungen/HFS durch Kühlung erfolgen

* Substanz- und regimeabhängig

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

Scalp Cooling:

1. 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.
2. Rugo HS, Voigt J. Scalp Hypothermia for Preventing Alopecia During Chemotherapy. A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Breast Cancer. 2018 Feb;18(1):19-28.
3. Rugo HS, Melin SA, Voigt J. Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis. Breast Cancer Res Treat. 2017 Jun;163(2):199-205.



Scalp Cooling: Scalp Cooling Alopecia Prevention Trial (SCALP) und Metaanalysen

AGO: +/- LOE 2b B

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

Primary Outcome: hair preservation

Cooling: 50.5 % success vs. 49.5 % failure

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

Fisher's exact test $p < 0.001$

Zwei Metaanalysen: AGO: +/- LOE 1b

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

- 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.
- Rugo HS, Voigt J. Scalp Hypothermia for Preventing Alopecia During Chemotherapy. A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Breast Cancer. 2018 Feb;18(1):19-28.
- Rugo HS, Melin SA, Voigt J. Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis. Breast Cancer Res Treat. 2017 Jun;163(2):199-205.



Nebenwirkungen nach Organsystemen Inzidenz, Prävention, Therapie

10. Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen *(siehe Kapitel Osteoonkologie)*

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,
AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)



Nebenwirkungen nach Organsystemen Inzidenz, Prävention, Therapie

11. Allgemeine Erkrankungen und Beschwerden am Verabreichungsort

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,
AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)



Paravasate mit potenziell nekrotisierenden Substanzen (Anthracycline, Taxane, Vinorelbine)

	Oxford		
	LoE	GR	AGO
• Dexrazoxane zur Behandlung von Anthracycliner-Paravasaten (Ausnahme liposomales A)	2b	B	++
• Hyaluronsäure zur Behandlung von Taxan/Vinorelbine-Paravasaten	3b	D	++

Relevant practice guideline:

1. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants.
2. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020, AWMF Registernummer: 032/054OL

Dexrazoxane

1. Hensley ML, Hagerty KL, Kewalramani T, et al.: Cardioprotective effect of dexrazoxane in patients with breast cancer treated with anthracyclines in adjuvant setting: a 10-year single institution experience. *J Clin Oncol.* 2009 Jan 1;27(1):127-45.
2. Testore F, Milanese S, Ceste M, et al.: Dexrazoxane (Totect): FDA review and approval for the treatment of accidental extravasation following intravenous anthracycline chemotherapy. *Oncologist.* 2008 Apr;13(4):445-50.
3. Mouridsen HT, Langer SW, Buter J, et al.: Treatment of anthracycline extravasation with Savene (dexrazoxane): results from two prospective clinical multicentre studies. *Ann Oncol.* 2007 Mar;18(3):546-50.

Hyaluronsäure

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Paravasate

Dexrazoxane/Hyaluronsäure

Dexrazoxane zur Behandlung von Anthracyclin-Paravasaten

Tag 1: 1000 mg/m² (max. 2000 mg), IV 1–2 Stunden

Tag 2: 1000 mg/m² (max. 2000 mg), IV 1–2 Stunden

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

In anderen Fällen bzw. in denen eine Therapie mit Dexrazoxan nicht indiziert ist, gelten für die Anthracyclin-Paravasate die folgenden Maßnahmen.

Lokale Kälte: Eispackung 6-stündlich jeweils für 15 Min. für 3 Tage oder: 24 h Abdeckung mit Eisbeuteln

Lokale Applikation von Dimethylsulfoxid (DMSO) 99% mit Watteträger 3- bis 4-stündig für mind. 3 Tage (besser 14 Tage) auftragen und an der Luft trocknen lassen. Das Intervall kann ab Tag 4 auf 6 Stunden verlängert werden.

Hyaluronsäure bei Taxan/Vinorelbine-Paravasaten:

- 1-10 Amp a 150 IU
- 1 ml Lösungsmittel (z.B. NaCl 0,9%)
- Lokalanästhesie
- Keine Thermotherapie bei Taxanen, trockene Wärme 4 x täglich 20 min bei Vincaalkaloiden

Relevant practice guideline

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,

AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)



- **Andere supportive und palliative Fragestellungen**

- Ermährung
- Schmerztherapie
- Palliative Care



Ernährungsmangel

Nährstoffmangel ist ein häufiges medizinisches Problem, das 15–40% der Krebspatienten betrifft. Es beeinträchtigt ihre Lebensqualität und kann den Erfolg der Behandlung beeinträchtigen.

- Integration der Ernährungsberatung in das klinische Management empfohlen
- Zur Ernährung siehe S3-Leitlinie Palliativmedizin und supportive Therapie

Klinische Ernährung:

1. Arends J, Bertz H, Bischoff SC, et al. und das DGEM Steering Committee. Klinische Ernährung in der Onkologie. S3-Leitlinie AWMF Reg.: 073-0061Aktuel Ernahrungsmed 2015; 40: e1–e74 [www.awmf.org/uploads/tx_szleitlinien/073-006I_S3_Klin_Ernährung_in_der_Onkologie_2015-10.pdf](http://www.awmf.org/uploads/tx_szleitlinien/073-006I_S3_Klin_Ern%C3%A4hrung_in_der_Onkologie_2015-10.pdf) abgerufen 2101202
2. de Las Peñas R, Majem M, Perez-Altozano J, et al SEOM clinical guidelines on nutrition in cancer patients (2018). Clin Transl Oncol. 2019 Jan;21(1):87-93. doi: 10.1007/s12094-018-02009-3. Epub 2019 Jan 8.
3. van den Berg MMGA1, Kok DE2, Posthuma L1, et al Breast Cancer Res Treat. 2019 Jan;173(2):475-481. doi: 10.1007/s10549-018-5014-5. Epub 2018 Oct 23.



Schmerztherapie

- **Nicht-Opioide; WHO Stufe 1**
Diclofenac resinat, Ibuprofen und / oder Metamizol, Paracetamol
- **Niedrig-potente Opioide; WHO Stufe 2**
Tramadol (vorzugsweise als Retard-Tabletten) bzw. Tilidin/ Naloxon (ebenfalls als Retard-Tabletten)
- **Hoch-potente Opioide; WHO Stufe 3**
Morphin, Buprenorphin (sublingual oder als transdermales System), Fentanyl (transdermales System), Hydromorphone, Oxycodon, als Reserve Levomethadon. Die notwendige Opioddosis wird schrittweise gegen den Schmerz titriert.
- **Koanalgetika**
Canabinoide, Gabapentin, Pregabalin, Carbamazepin, Amitriptylin, Bisphosphonate

Relevant practice guideline:

1. WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. Januar 2019 , Geneva ISBN: 978-92-4-155039-0 www.who.int/ncds/management/palliative-care/cancer-pain-guidelines/en/ Zugriff 21.01.2020

Relevant practice guideline:

1. Horlemann J, Schürmann N. DGS Praxisleitlinien in der Schmerztherapie. Cannabis in der Schmerzmedizin v 1.0 www.dgs-praxisleitlinien.de/index.php/leitlinien/cannabis



Palliative Versorgung

- Allen Patienten soll nach der Diagnose einer nicht-heilbaren Krebserkrankung Palliativversorgung angeboten werden, unabhängig davon, ob eine tumorspezifische Therapie durchgeführt wird.
- Spezialisierte Palliativversorgung soll in onkologische Entscheidungsprozesse integriert werden, z. B. durch Beteiligung an interdisziplinären Tumorkonferenzen.
- Patienten mit einer nicht-heilbaren Krebserkrankung, die in Strukturen der spezialisierten Palliativmedizin betreut werden (Palliativstation, ambulante spezialisierte Versorgung wie z. B. SAPV) sollen Zugang zu onkologischer Beratung haben.

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

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung, Lang- version 2.0, 2019, AWMF-Registernummer: 128/001OL, <https://www.leitlinienprogramm-onkologie.de/leitlinien/palliativmedizin/> (abgerufen am: 21.01.2020)