

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. Thomssen 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 2002–2019:**

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

- **Version 2020:**

Müller / Albert

Inhaltsverzeichnis

- **Leitlinien**
- **Toxizitätsbeurteilung**
- **Inzidenz von Nebenwirkungen
(nach Fachinformationen; MedDRA-Standard)**
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 - Inzidenz, Prävention, Therapie
- **Substanzspezifische Nebenwirkungen**
 - Zielgerichtete Substanzen
- **Andere Fragestellungen**
 - Schmerztherapie, Palliative Care

■ Leitlinien - Umfeld

| | |
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|  <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p> | <h2 style="text-align: center;">Leitlinien – Umfeld</h2> <p>Nationale und internationale spezifische Leitlinien befassen sich mit verschiedenen Aspekten der evidenzbasierten supportiven Therapie von Karzinompatientinnen und -patienten</p> <p>Ohne Anspruch auf Vollständigkeit werden derartige (bes. deutsche) Leitlinienwerke genannt</p> <p>Hier soll insbesondere auf die Aspekte Wert gelegt werden, die Brustkrebspatientinnen betreffen:</p> <ul style="list-style-type: none"> ▪ S3-Leitlinie: Supportive Therapie bei onkologischen Patientinnen Langversion 1.2 – November 2019 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)**



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Toxizitäts-Beurteilung

Akute Toxizität (nach WHO¹ oder NCI-CTC²)

Akute Toxizität nach jedem Therapiezyklus abfragen und dokumentieren

| Grad | Notwendige Informationen |
|-------------------------|---------------------------------|
| 0 keine | Beteiligte Organe |
| 1 mild | Art der Toxizität |
| 2 mäßig | Zeitintervall nach Behandlung |
| 3 ausgeprägt | Effekt auf den Allgemeinzustand |
| 4 lebensbedrohlich | Behandlungsnotwendigkeit |
| 5 therapiebedingter Tod | Erreichen einer Verbesserung |

LoE 5 D AGO ++

Langzeittoxizität (=Sekundärerkrankungen nach Tumorthherapie)

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

LoE 5 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.



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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)



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- **Nebenwirkungshäufigkeiten
(nach Angaben in den Fachinformationen
gemäß MedDRA*)**

* MedDRA - Medical Dictionary for Regulatory Activities

*MedDRA - Medical Dictionary for Regulatory Activities

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

Chemotherapie – Akute Toxizitäten I

| Substanz | Systemorganklasse | | | | | | | | | | | |
|--------------------------------------|--|---------------------------------|-------------------|---------------------------|-----------------------------|---------------------------------------|--------------------------------|-----------------------------------|---------------|---|------------------|---------------|
| | Infektionen und parasitäre Erkrank. | Neubildungen, sek. Malignome | Blut, Lymphsystem | Immunsystem, Allergien | Endokrine Erkrank- ungen | Stoffwechsel- und Ernährungs-Stör. | Psychiatrische Erkrankungen | Erkrankungen des Nervensystems | Augenerkrank. | Erkrank. des Ohrs und des Labyrinths | Herzerkrankungen | Gefäßerkrank. |
| Alkylantien | | | | | | | | | | | | |
| Cyclophosphamid | 4 | 2 | 5 | 5 | 1 | - | 1 | 3 | 2 | 3 | 3 | 3 |
| Antimetabolite | | | | | | | | | | | | |
| Methotrexat | 1 | - | 4 | 3 | 3 | - | 3 | 4 | 2 | - | 1 | 2 |
| 5-Fluorouracil* | 5 | - | 5 | 2 | 2 | 5 | - | 3 | 3 | - | 5 | 3 |
| Capecitabin | 4 | 3 (Lipom) | 4 | 3 | - | 5 | 4 | 4 | 4 | 3 | 3 | 4 |
| Gemcitabin | 4 | - | 5 | 1 | - | 4 | - | 4 | - | - | 2 | 2 |
| Platin-Komplexe | | | | | | | | | | | | |
| Cisplatin | 4 | 2 | 5 | 3 | 2 | 5 | - | 4 | 2 | 5 | 4 | 4 |
| Carboplatin | 4 | - | 5 | 4 | - | - | - | 4 | 4 | 4 | 4 | - |
| Anthrazykline / Anthrachinone | | | | | | | | | | | | |
| Epi-/Doxorubicin | 5 | 3 | 5 | 1-2 | - | 1-5 | - | - | 4 | - | 4 | 5 |
| Liposom. Doxorubicin | 5 | - | 5 | - | - | 5 | 3 | 4 | (4) | - | 4 | 4 |
| PEG-lipos. Doxorubicin | 4 | - | 4 | - | - | 5 | - | 4 | 4 | - | 4 | - |
| Mitoxantron | 5 | 3 | 5 | 3 | - | 4 | - | 4 | 3 | 3 | 4 | 3 |
| Taxane | | | | | | | | | | | | |
| Paclitaxel | 5 | 1 | 5 | 5 | - | 1 | 1 | 5 | 1 | 1 | 4 | 5 |
| nab-Paclitaxel | 4 | - | 5 | 3 | - | 5 | 4 | 5 | 4 | 4 | 4 | 4 |
| Docetaxel | 5 | - | 5 | 5 | - | 5 | - | 5 | - | - | 4 | 4 |
| Andere Spindelgifte | | | | | | | | | | | | |
| Vinorelbin IV (PO) | 5(5) | - | (5) | 2(-) | - | - | (-5) | (-5) | (-4) | - | 2(3) | 3(4) |
| Eribulin | 4 | - | 4 | - | - | 5 | 4 | 5 | 4 | 4 | 4 | 4 |

Die Liste und Graduierung der Nebenwirkungen ist nach Systemorganklassen, MedDRA-Terminologie und den folgenden Häufigkeitskategorien dargestellt:
 1. Sehr selten (<1/10.000); 2. Selten (≥ 1/1.000 bis < 1/10.000); 3. Gelegentlich (≥ 1/1.000 bis < 1/100); 4. Häufig (≥ 1/100 bis < 1/10); 5. Sehr häufig (≥ 1/10).
 - Nicht bekannt (Häufigkeit 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-Injektionsloesung-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=eebfb22e78f1cc8d9935d59c087e80630146f49e>

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/Abbraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension_514889/fachinformation

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

Vinorelbin: <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 Antitubercular Drugs and Cardioprotection:e12-e18. Review.

Chemotherapie – Akute Toxizitäten II

| Substanz | Systemorganklasse | | | | | | | | | | Besonderheiten |
|-------------------------------|--------------------------------------|---------------------------------------|-------------------------------|---|--|------------------------------|--|---|--|-------------------------------------|---|
| | Erf. d. Atemwege, Brustraum, Mediast | Erf. d. GI-Traktes (Übelk./Erbrechen) | Leber- und Gallenerkrankungen | Erf. d. Haut/Unterhaut (inkl. Alopecia) | Skelettmus- , Bindegew.- u. Knochenerkr. | Erf. der Nieren und Harnwege | Schwang.-, Wochenbett u. perinatale E. | Erf. d. Geschlechtsorgane u. Brustdrüse | Allg. Erf. u. Beschw. am Applikationsort | Kongenit.-, famili. und genet. Erf. | |
| Alkylantien | | | | | | | | | | | |
| Cyclophosphamid | 2 | 4 | 4 | 5 | - | 5 | - | 4 | 5 | - | Hyponatriämie |
| Antimetabolite | | | | | | | | | | | |
| Methotrexat | 4 | 5 | 5 | 4 | 3 | 3 | - | 3 | 1 | - | Mukositis, Risiko "third space"-Toxizität |
| 5-Fluorouracil | 5 | 5 | 3 | 5 | - | - | - | - | 5 | - | Risiko DPD-Mangel: leicht 5%, schwer 0,1%; Diarrhoe, Herz |
| Capecitabin | 4 | 5 | 4 | 5 | 4 | 3 | - | 3 | 5 | - | Hand-Fuß-Syndrom (HFS), Risiko DPD-Mangel; Herz |
| Gemcitabin | 5 | 5 | 5 | 5 | 4 | 5 | - | - | 5 | - | Flu-like Symptome, Ödeme, Herz |
| Platin-Komplexe | | | | | | | | | | | |
| Cisplatin | 4 | 5 | 4 | 4 | - | 5 | - | 3 | 5 | - | Nierentoxizität, Ototoxizität, CIPN Kollitis, (Nierentox.) |
| Carboplatin | 4 | 5 | - | 4 | 4 | 4 | - | - | 4 | - | |
| Anthrazykline / Anthrachinone | | | | | | | | | | | |
| Epi-/Doxorubicin | 2 | 5 | - | 5 | 1 | 4 | - | 1 | 5 | - | Kardiotoxizität (CHF), sek. Malignome, Paravast |
| Lipo. Doxorubicin | 4 | 5 | 4 | 5 | 4 | 3 | - | (4) | 5 | - | |
| PEG-lipo. Doxo. | 4 | 5 | - | 5 | 4 | - | - | 4 | 5 | - | Palmares und plantares Erythem (PPE) |
| Mitoxantron | 4 | 5 | 3 | 5 | - | 3 | - | 3 | 4 | - | Sek. AML, Kardiomyopathie |
| Taxane | | | | | | | | | | | |
| Paclitaxel | 2 | 5 | 1 | 5 | 5 | - | - | - | 5 | - | Periphere Neuropathie (CIPN); Hypersensit., Myalgien |
| nab-Paclitaxel | 4 | 5 | 3 | 5 | 5 | 3 | - | 3 | 5 | - | Periphere Neuropathie (CIPN) |
| Docetaxel | 5 | 5 | - | 5 | 5 | - | - | - | 5 | - | Fluid retention, Paronychie, Kollitis, Myalgie |
| Andere Spindelgifte | | | | | | | | | | | |
| Vinorelbin IV (PO) | 3(4) | 2 (5) | 5(4) | 2(5) | -(4) | 2(4) | - | - | - | - | Phlebitis, GI-Tox (PO), CIPN Obstipation, CIPN |
| Eribulin | 5 | 5 | 4 | 5 | 5 | 4 | - | - | 5 | - | |

Die Liste und Graduierung der Nebenwirkungen ist nach Systemorganklassen, MedDRA-Terminologie und den folgenden Häufigkeitskategorien dargestellt:
 1. Sehr selten (<1/10.000); 2. Selten (≥ 1/1.000 bis < 1/10.000); 3. Gelegentlich (≥ 1/1.000 bis < 1/100); 4. Häufig (≥ 1/100 bis < 1/10); 5. Sehr häufig (≥ 1/10).
 - 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-Injektionsloesung-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?elD=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/Abbraxane-5-mg-ml-Pulver-zur-Herstellung-einer-Infusionssuspension_514889/fachinformation
 Docetaxel: <https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d>
 Vinorelbin: <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
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- breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet*. 2011;377:914-23
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Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

1. Infektionen u. parasitäre Erkrankungen

- Allgemeine Infektionsprophylaxe
- Hepatitis B-Screening



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Allgemeine Infektionsprophylaxe

NB nur selten für solide Tumoren wie MaCa anwendbar

ASCO Practice Guideline „Antimicrobial Prophylaxis...” 2018

| | Oxford | | |
|--|--------|----|-----|
| | LoE | GR | AGO |
| ▪ Vermeidung von besonders infektionsbegünstigenden Faktoren/Umgebungen | 5 | D | + |
| ▪ Prophylaktische Therapie in Low-Risk-Patienten | 1a | B | - |
| ▪ Prophylaktische Therapie bei Hochrisikopatienten* (z.B. gemäß NCCN-Leitlinien) mit: | | | |
| ▪ Antibiotika | 1a | A | ++ |
| ▪ Antimykotika (Triazol-Antimykotika) | 1a | B | +/- |
| ▪ Virostatika bei soliden Tumoren | 5 | D | - |
| ▪ Granulopoese-stimulierende Faktoren | 1a | A | ++ |


* Definition Hochrisiko: vermutete Neutropeniedauer < 100/μl ≥ 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



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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



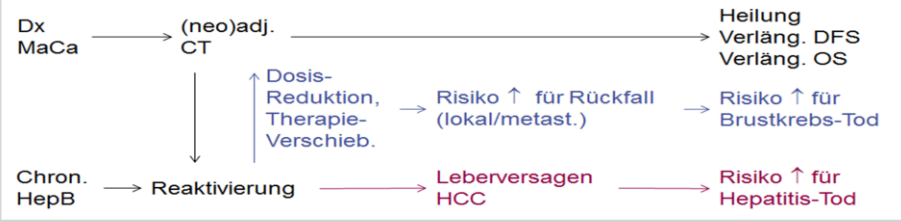
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Interaktion Hepatitis und Tumorbehandlung

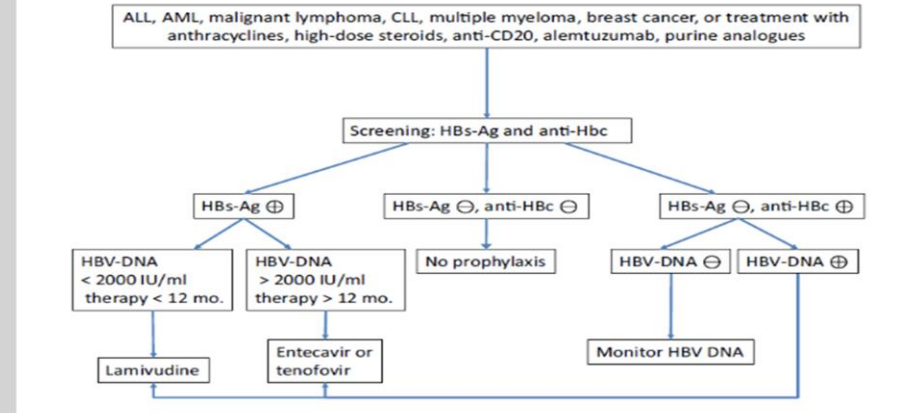


„Number needed to screen“ in Deutschland:

| | |
|---------------------------------|-------------|
| Prävalenz 0,5%-1% (allg. Bev.): | 100 bis 200 |
| Prävalenz 3,6% (Migranten): | 28 |


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AGIHO / DGHO – Empfehlungen zum Hepatitis B-Screening in der Onkologie



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

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Arbeitsgemeinschaft
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Internationale Screening Empfehlungen – Hepatitis B

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

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



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

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Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

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

|  ARBEITSGEMEINSCHAFT GYNÄKOLOGISCHE ONKOLOGIE e.V.  100-110 © AGO e. V. in der DGGG e.V. sowie in der DKG e.V. Guidelines Breast Version 2020.1D www.ago-online.de FORSCHEN LEHREN HEILEN | Sekundäre Malignome I | |
|--|-----------------------|--|
| | Oxford LoE GR | |
| <ul style="list-style-type: none"> ▪ Die Induktion von soliden, malignen Tumoren durch Chemotherapie ist selten ▪ Alkylantien erhöhen dosisabhängig das Risiko für Leukämien auf 0,2–0,4 % innerhalb von 10–15 Jahren ▪ Anthrazyklinhaltige Regime erhöhen das Risiko für MDS und Leukämie auf 0,2–1,7 % innerhalb von 8–10 Jahren ▪ PARP-Inhibitoren sind assoziiert mit einem erhöhten Risiko für AML und MDS von 0,5–1% ▪ Radiotherapie erhöht das Risiko einer Leukämie bei Pat. mit einer anthrazyklinhaltigen Therapie um 0,2–0,4 % ▪ Tamoxifen verdoppelt das Risiko für die Entwicklung eines Endometriumkarzinoms (bei Therapiebeginn ab 55. Lj.) | 2a | |
| | 2a | |
| | 2a | |
| | 2b | |
| | 2b | |
| | 2b | |

Statements 1-4

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Tamoxifen and endometrial cancer

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Sekundäre Malignome II (nach Radiotherapie)

Oxford
LoE

| | |
|--|---|
| <ul style="list-style-type: none"> ▪ 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) | <p style="color: green;">1a</p> <p style="color: green;">2b</p> <p style="color: green;">2c</p> |
|--|---|

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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) | | | |
|--|--------|----|-----|
| | Oxford | | |
| | LoE | GR | AGO |
| ▪ Indiziert bei asymptomatischer Anämie | 1a | B | - |
| ▪ Therapie und sekundäre Prophylaxe bei CT-induzierter Anämie | 1a | A | + |
| ▪ Adjuvante Situation | 1b | A | + |
| ▪ Neoadjuvante/metastasierte Situation | 1a | A | +/- |
| ▪ Bei dosisdichter/dosiseskalierter CT (iddETC) | 1b | A | + |
| ▪ Therapie beginnt bei Hb-Werten < 10g/dl | 1a | A | + |
| ▪ Ziel-Hb 11–12 g/dL | 1a | A | + |
| ▪ Verbesserung der Prognose (krankheitsfreies Intervall, Gesamtüberleben) | 1a | B | -- |
| ▪ ESF erhöht das Risiko von thromboembolischen Komplikationen | 1a | A | |

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Leitlinie:

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)

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Relevante Leitlinien

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

N=2.098 Pat., Hb <11g/dl; non inferiority study.
Prespecified upper non inferiority margin = 1.15

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

* Investigator determined
 ** Independent review committee
J Clin Oncol 2016 (34): 1197-1209

1. Leyland-Jones B, Bondarenko I et al. J Clin Oncol 2016 (34): 1197-1209



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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.**


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Relevante Leitlinien

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(https://www.nccn.org/professionals/physician_gls/pdf/anemia.pdf)

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| | Oxford | | |
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| | LoE | GR | AGO |
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| <ul style="list-style-type: none"> Primäre Prophylaxe für eine zu erwartende febrile Neutropenie (FNP) <ul style="list-style-type: none"> Bei Risiko für FNP 10–20 % <ul style="list-style-type: none"> Im Falle zusätzlicher individueller Risiken Bei FNP-Risiko > 20 % (e.g. DAC, dosisdichte CT) Sekundäre Prophylaxe während der Chemotherapie (frühere FNP oder Neutropenie Grad IV > 7 Tage) Therapeutischer Nutzen bei FNP Beginn der Therapie in Verbindung mit Art und Dauer der Chemotherapie <ul style="list-style-type: none"> Pegfilgrastim Tag 2 Lipegfilgrastim Tag 2 Filgrastim/Lenograstim von Tag 2–5 bis absolute Neutrophilenzahl > 2–3 x 10⁹ | 1b 3b 1a 1b 1a 1b 1b 1b | B C A A A A A A | +/- + ++ ++ +/- ++ ++ ++ |

Relevante Leitlinien


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
2. NCCN Guidelines 2020
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Statements 1-4

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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 Niedrigrisikopat. 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 | +/- |

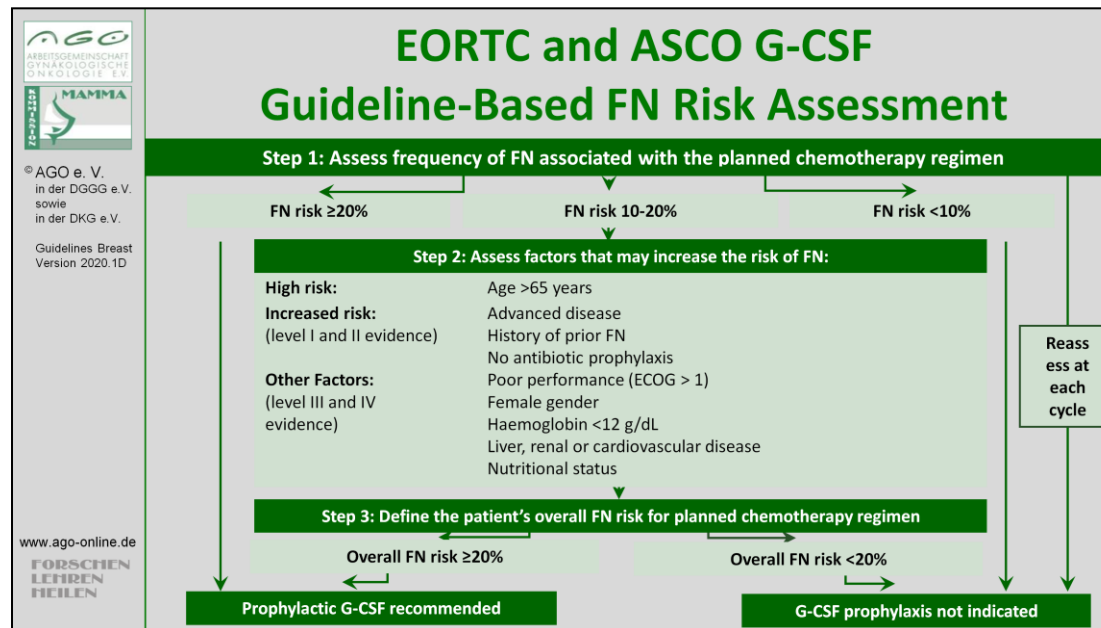
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|  <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p> | <h2 style="color: green; text-align: center;">Empirische Antibiotikatherapie</h2> <p>Die Empfehlungen zur empirischen Antibiotikatherapie unterliegen einem infektionsbiologisch bedingten Wechsel und bedürfen der beständigen fachkundigen Anpassung.</p> <p>Die Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de gibt aktuelle Hinweise.</p> |
|--|--|

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

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Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

4. Endokrine Erkrankungen

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|--|---|--|
| | <ul style="list-style-type: none"> ▪ Eine CRA kann dauerhaft oder vorübergehend sein (abhängig vom Alter der Pat. und der Art der Chemotherapie) ▪ Das Risiko der CRA steigt mit dem Alter / Therapiedauer ▪ CRA ist ein (unsicherer) Surrogatmarker für Menopause und Fertilität ▪ Eine adjuvante endokrine Therapie mit einem GnRHa induziert eine reversible Amenorrhoe, und verschiebt eine Konzeption in eine weniger fertile Phase ▪ Die Ovarialreserve der nach Chemotherapie prämenopausal gebliebenen Frauen ist reduziert ▪ CRA ist mit einer verbesserten Prognose (DFS/OS) assoziiert <p>Synonyma: Chemotherapie / Therapie-induzierte Amenorrhoe (TIA/CIA)</p> | <p>Oxford LoE</p> <p>2b</p> <p>2b</p> <p>5</p> <p>5</p> <p>2b</p> <p>1b</p> |

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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 |
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Statements 1-4

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| (Therapie assoziierte) Fatigue | | | |
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| | Oxford | | |
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| ▪ Fatigue häufiges Symptom bei Brustkrebspatientinnen (30–60%) | 2a | B | |
| ▪ Ausschluss anderer Ursachen (Anämie, Tumorausdehnung, Begleiterkrankungen, Medikamente) für Fatigue | 1a | A | ++ |
| ▪ Gezielte psychosoziale Interventionen können Fatigue lindern | 1a | A | ++ |
| ▪ Körperliches Training kann Fatigue verbessern | 1b | D | + |
| ▪ Diät, Yoga können Fatigue verbessern | 2b | B | + |
| ▪ Methylphenidate kann Fatigue verbessern | 1a | D | + |

Fatigue is frequently present...

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(Therapie-assoziierte) Kognitive Störungen

| Oxford | |
|--------|----|
| LoE | GR |
| 2a | B |
| 2b | B |
| 3a | C |
| 1a | B |

- **Therapiebedingte kognitive Störungen (sog. „Chemobrain“) häufig beschrieben (16–75%)**
- **Verhaltenstherapie kann kognitive Funktion verbessern**
- **Methylphenidate kann kognitive Funktion bei Patientinnen mit Krebs verbessern**
- **Unter Aromatasehemmertherapie wurden kognitive Störungen beobachtet (insbes. Wortgedächtnis)**

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

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Verhaltenstherapie kann kognitive Funktion verbessern

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Methylphenidate kann kognitive Funktion bei Patientinnen mit Krebs verbessern

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Unter Aromatasehemmertherapie wurden kognitive Störungen beobachtet

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(Therapie assoziierte) Schlafstörungen

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

- **Schlafstörungen häufig bei Mammakarzinompatientinnen 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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Behavioral therapies have demonstrated efficacy.....

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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)

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(18):1941-67.
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Chemotherapie-induzierte periphere Neuropathie – Prävention –

| | Oxford | | |
|---|-----------------|----|-----|
| | LoE | GR | AGO |
| <u>Nicht-medikamentöse Prävention</u> | | | |
| ▪ Funktionstraining (Fitness, sensomotorisches Stimulationstraining etc.) | 5 | D | + |
| ▪ Kompressionstherapie (chirurgische Handschuhe, Kompressionsstrümpfe) | 2b | B | + |
| ▪ Kühlhandschuhe und Kühlstrümpfe | 2b ^a | B | +/- |
| ▪ Elektro-Akupunktur | 1b | B | - |

Medikamentöse Prävention

| | | | |
|---|----|---|-----|
| ▪ Venlafaxin | 2a | C | +/- |
| ▪ Palmitoylethanolamid (PEA) topisch oder p.o. | 5 | D | +/- |
| ▪ Alpha-Liponsäure, Amifostin, Amitriptylin, Acetyl-L-Carnitin, Carbamazepin, Elektrolytlösungen, Glutathion, Goshajinkigan (GJG), Oxcarbazepin, Vitamin B, Vitamin E oder andere Substanzen ¹ | 1b | A | - |

¹ Liste nicht empfohlener Medikamente bei Hershman et al. 2014

Reviews/Leitlinien

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Nicht-medikamentöse Prävention

Funktionstraining

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Kompression

1. Tsuyuki S, Senda N, Kanng Y, et al.: Evaluation of the effect of compression therapy using surgical gloves on nanoparticle albumin-bound paclitaxel-induced peripheral neuropathy: a phase II multicenter study by the Kamigata Breast Cancer Study Group. Breast Cancer Res Treat. 2016 Nov;160(1):61-67.
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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>.

2. Sundar R, Bandla A, Tan SS, et al.: Limb Hypothermia for Preventing Paclitaxel-Induced Peripheral Neuropathy in Breast Cancer Patients: A Pilot Study. *Front Oncol*. 2017 Jan 10;6:274.

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

1. Aziz MT, Good BL, Lowe DK. Serotonin-norepinephrine reuptake inhibitors for the management of chemotherapy-induced peripheral neuropathy. *Ann Pharmacother*. 2014 May;48(5):626-32.
2. Durand JP, Deplanque G, Montheil V, et al.: Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. *Ann Oncol*. 2012 Jan;23(1):200-5
3. Gallagher HC, Gallagher RM, Butler M, et al.: Venlafaxine for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2015 Aug 23;(8):CD011091.

Palmitoylethanolamid (PEA)

1. Lombardi G, Miglio G, Varsaldi F, et al.: Oxyhomologation of the amide bond potentiates neuroprotective effects of the endolipid N-palmitoylethanolamine. *J Pharmacol Exp Ther*. 2007 Feb;320(2):599-606
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Verschiedene Substanzen

1. Schloss J, Colosimo M, Vitetta L. Herbal medicines and chemotherapy induced peripheral neuropathy (CIPN): A critical literature

- review. Crit Rev Food Sci Nutr. 2017 Apr 13;57(6):1107-1118.
2. Schloss JM, Colosimo M, Airey C, et al.: Nutraceuticals and chemotherapy induced peripheral neuropathy (CIPN): a systematic review. Clin Nutr. 2013 Dec;32(6):888-93.
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 5. Schloss JM, Colosimo M, Airey C, et al.: A randomised, placebo-controlled trial assessing the efficacy of an oral B group vitamin in preventing the development of chemotherapy-induced peripheral neuropathy (CIPN). Support Care Cancer. 2017 Jan;25(1):195-204.
 6. Leal AD, Qin R, Atherton PJ, et al.: Alliance for Clinical Trials in Oncology. North Central Cancer Treatment Group/Alliance trial N08CA-the use of glutathione for prevention of paclitaxel/carboplatin-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled study. Cancer. 2014 Jun 15;120(12):1890-7
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Acetyl-L-Carnitin

1. Hershman DL, Unger JM, Crew KD, et al.: Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. J Clin Oncol. 2013 Jul 10;31(20):2627-33.
2. Hershman DL, Unger JM, Crew KD, et al.: Two-Year Trends of Taxane-Induced Neuropathy in Women Enrolled in a Randomized Trial of Acetyl-L-Carnitine (SWOG S0715). J Natl Cancer Inst. 2018 Jan 18.

Chemotherapie-induzierte periphere Neuropathie – Therapie –

Nicht-medikamentöse Therapie

- Funktionstraining (Fitness, sensomotorisches Stimulationstraining etc.)
- Physiotherapie / physikalische Therapie
- Akupunktur

Medikamentöse Therapie

- Menthol lokal (1%), Capsaicin/Lidocain lokal
- Baclofen/Amitriptylin/Ketamin-Creme
- Duloxetine zur Behandlung von Schmerzen durch CIPN
- Opioide zur Behandlung von Schmerzen durch CIPN
- Palmitoylethanolamid (PEA) topisch oder p.o.
- Venlafaxin
- Gabapentin, Pregabalin
- Amitriptylin/ Nortriptylin, Imipramin/Desipramin
- Acetyl-L-Carnitin, Lamotrigin oder andere Substanzen¹

¹ Liste nicht empfohlener Medikamente bei Hershman et al. 2014

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

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(18):1941-67.
2. Hu LY, Mi WL, Wu GC, et al.: Prevention and Treatment for Chemotherapy-Induced Peripheral Neuropathy: Therapies Based on CIPN Mechanisms. Current Neuropharmacology, 2018, 16, 1-12
3. Majithia N, Temkin SM, Ruddy KJ, et al.: National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: outcomes and lessons. Support Care Cancer. 2016 Mar;24(3):1439-47. doi: 10.1007/s00520-015-3063-4. Epub 2015 Dec 19.
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5. Majithia N, Loprinzi CL, Smith TJ. New Practical Approaches to Chemotherapy-Induced Neuropathic Pain: Prevention, Assessment, and Treatment. Oncology (Williston Park). 2016 Nov 15;30(11):1020-9. Review.
6. Pachman DR, Barton DL, Watson JC, et al.: Chemotherapy-induced peripheral neuropathy: prevention and treatment. Clin Pharmacol Ther. 2011 Sep;90(3):377-87.
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chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial." JAMA 309(13): 1359-1367.

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Nicht-medikamentöse Therapie

Funktionstraining

1. Duregon F, Vendramin B, Bullo V, et al.: Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review. Crit Rev Oncol Hematol. 2018 Jan;121:90-100.
2. Smith TJ, Razzak AR, Blackford AL, Ensminger J, Saiki C, Longo-Schoberlein D, Loprinzi CL: A pilot randomized sham-controlled trial of mc5-a scrambler therapy in the treatment of chronic chemotherapy-induced peripheral neuropathy (cipn). Journal of palliative care 2020;35:53-58.
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4. Lu W, Giobbie-Hurder A, Freedman RA, Shin IH, et al.: Acupuncture for chemotherapy-induced peripheral neuropathy in breast cancer survivors: A randomized controlled pilot trial. Oncologist 2019.

Medikamentöse Therapie

Menthol / Capsaicin

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Baclofen/Amitryptilin/Ketamin-Creme

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Palmitoylethanolamid (PEA)

1. Lombardi G, Miglio G, Varsaldi F, et al.: Oxyhomologation of the amide bond potentiates neuroprotective effects of the endolipid N-palmitoylethanolamine. *J Pharmacol Exp Ther*. 2007 Feb;320(2):599-606

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Venlafaxin

1. Aziz MT, Good BL, Lowe DK. Serotonin-norepinephrine reuptake inhibitors for the management of chemotherapy-induced peripheral neuropathy. Ann Pharmacother. 2014 May;48(5):626-32.
2. Durand JP, Deplanque G, Montheil V, et al.: Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFOX, a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol. 2012 Jan;23(1):200-5
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Gabapentin, Pregabalin:

1. Rao RD, Michalak JC, Sloan Jaet al.: Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). Cancer. 2007 Nov 1;110(9):2110-8.
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Amitriptylin/Nortriptylin

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Acetyl-L-Carnitin, Lamotrigin oder andere Substanzen:

1. Rao RD, Flynn PJ, Sloan JA, et al.: Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled trial, N01C3. *Cancer*. 2008 Jun 15;112(12):2802-8
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13. Duregon F, Vendramin B, Bullo V, et al.: Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review. *Crit Rev Oncol Hematol*. 2018 Jan;121:90-100.
14. The prescription of medical cannabis by a transitional pain service to wean a patient with complex pain from opioid use following liver transplantation: a case report.

15. Meng H, Hanlon JG, Katznelson R, et al. Can J Anaesth. 2016 Mar;63(3):307-10.
16. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage. 2014 Jan;47(1):166-73.
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FORSCHEN
LEHREN
HEILEN

Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

7. Herzerkrankungen

| | Oxford | | |
|---|---|---|--|
| | LoE | GR | AGO |
| <p>Äquivalente Kardiotoxizität von Doxorubicin und Epirubicin in den empfohlenen Dosierungen (450-500 bzw. 900-1000 mg/m² kum. Dosis)</p> <p>Weniger Kardiotoxizität nach liposomalem Doxorubicin</p> <p>Risikofaktoren für Anthrazyklin- oder Trastuzumab-assoziierte Kardiotoxizität</p> <ul style="list-style-type: none"> Alter, Übergewicht, Hypertonus, Hypercholesterinämie, Vorbestehende Herzerkrankungen (inkl. grenzwertige LVEF), Diabetes mellitus <p>Überwachung der Herzfunktion:</p> <p>Standardisierte Echokardiographie (LVEF oder SF in %)</p> <ul style="list-style-type: none"> Troponin I als Marker für Kardiotoxizität <p>Betablocker-Prophylaxe während Anthrazyklin-Therapie</p> | <p>2b</p> <p>1b</p> <p>2b</p> <p>3b</p> <p>2b</p> <p>2a</p> | <p>B</p> <p>B</p> <p>B</p> <p>C</p> <p>B</p> <p>B</p> | <p></p> <p></p> <p></p> <p>+</p> <p>+/-</p> <p>+/-</p> |

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 derivatives 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
2. 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.

“Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors.”

1. Serrano C, Cortés J, De Mattos-Arruda L, et al.: Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. Ann Oncol. 2011 Aug 9.

2. de Azambuja E, Ponde N, Procter M, et al: A pooled analysis of the cardiac events in the trastuzumab adjuvant trials. *Breast Cancer Res Treat* 2019.
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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6. Sautter-Bihl ML, Souchon R, Gerber B: Adjuvant therapy for women over age 65 with breast cancer. *Dtsch Arztebl Int* 108:365-371, 2011

“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.
2. Slamon D: Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med.* 2011 Oct 6;365(14):1273-83
3. Verma S: Is cardiotoxicity being adequately assessed in current trials of cytotoxic and targeted agents in breast cancer? *Ann Oncol.* 2011 May;22(5):1011-8. Epub 2010 Nov 22..
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6. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail.* 2016 Sep;22(9):659-69. doi: 10.1016/j.cardfail.2016.07.001. Epub 2016 Jul 6.
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8. Drafts BC, Twomley KM, D'Agostino R Jr, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. *JACC Cardiovasc Imaging*. 2013 Aug;6(8):877-85. doi: 10.1016/j.jcmg.2012.11.017. Epub 2013 May 1.
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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 \pm 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.
3. Kalam K, Marwick TH. Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: a systematic review and meta-analysis. *Eur J Cancer*. 2013 Sep;49(13):2900-9.



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LEHREN
HEILEN


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 |
| <u>Kardiale Toxizität</u> | | | |
| ▪ Trastuzumab simultan zur Radiotherapie | 2b | B | + |
| ▪ Trastuzumab simultan zu Epirubicin | 2b | B | +/- |
| ▪ Trastuzumab simultan zu Doxorubicin | 2b | B | - |
| ▪ Anthrazykline simultan zur Radiotherapie | 2c | C | - |
| <u>Risiko Lungen- / Brustparenchymfibrosen</u> | | | |
| ▪ Tamoxifen simultan zu Radiotherapie | 3 | C | +/- |
| ▪ Chemotherapie simultan zu Radiotherapie | 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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“Trastuzumab simultaneous to epirubicin”

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“Trastuzumab simultaneous to doxorubicin”

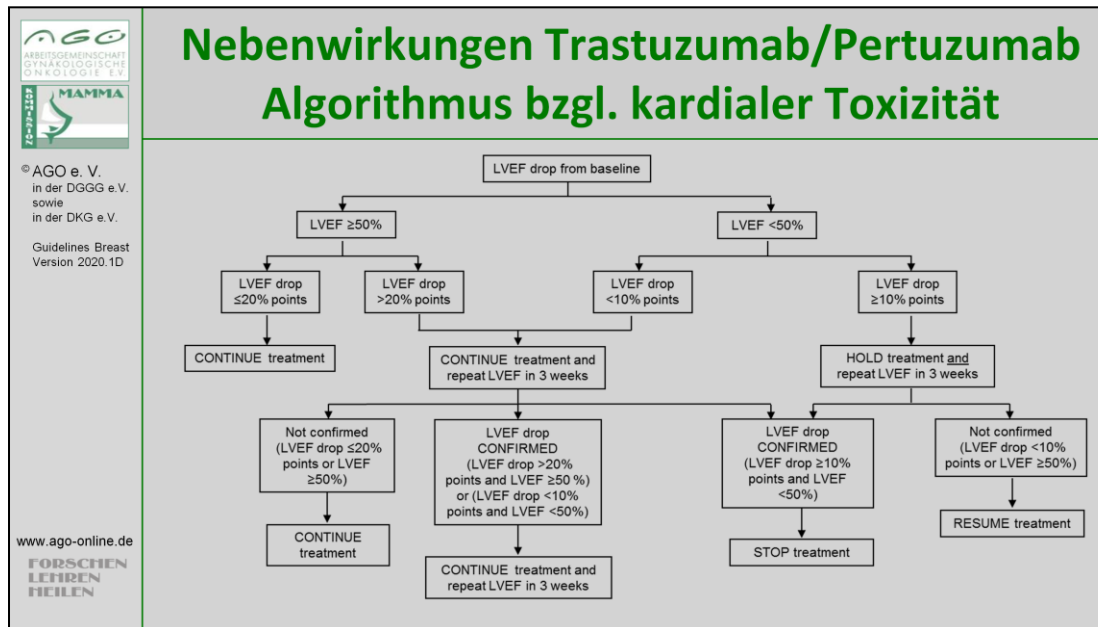
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“Anthracycline simultaneous to radiotherapy”

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”

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Nebenwirkungen nach Organsystemen

Inzidenz, Prävention, Therapie

8. Erkrankungen des Gastrointestinaltrakts

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



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<https://www.mascc.org>

| | Oxford | | |
|--|--------|----|-----|
| | LoE | GR | AGO |
| ▪ Abschätzen des emetogenen Potenzials des jeweiligen Chemotherapie-Protokolls | 5 | D | ++ |
| ▪ Neurokinin-1-Rezeptor-Antagonisten | 1b | A | ++ |
| ▪ Dexamethason | 1a | A | ++ |
| ▪ 5-HT ₃ -Antagonisten | 1b | A | ++ |
| ▪ Feste Kombination mehrerer Substanzen | 1b | A | ++ |
| ▪ Reserveantiemetika (Rescue Medication) | | | |
| ▪ Olanzapin | 1b | A | + |
| ▪ Levomepromazin, Benzodiazepine | 3b | C | + |
| ▪ Cannabinoide, Ingwer | | | |

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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, 2019DOI:[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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ACUTE Nausea and Vomiting: SUMMARY

| EMETIC RISK GROUP | ANTIEMETICS | | | | | | |
|-----------------------------------|------------------------|----|-----|-----|--------------------------|--|-----|
| High Non-AC | 5-HT ₃ | + | DEX | + | NK ₁ +/- OLZ* | | |
| High AC | 5-HT ₃ | + | DEX | + | NK ₁ +/- OLZ* | | |
| Carboplatin | 5-HT ₃ | + | DEX | + | NK ₁ | | |
| Moderate (other than carboplatin) | 5-HT ₃ | + | DEX | | | | |
| Low | 5-HT ₃ | or | | DEX | or | | DOP |
| Minimal | No routine prophylaxis | | | | | | |

5-HT₃ = serotonin receptor antagonist

DEX = DEXAMETHASONE



NK₁ = neurokinin receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA (combination of netupitant and palonosetron)

OLZ = OLANZAPINE


DOP = dopamine receptor antagonist

NOTE: If the NK₁ receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT₃ receptor antagonist.
* OLZ: Olanzapine may be added particularly if nausea is a concern.

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DELAYED Nausea and Vomiting: SUMMARY

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

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

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| Supportive Therapie Antiemetika | | | | |
|---|--|---|---|-----------|
| Wirkstoffgruppe | Substanz | Dosierung | Nebenwirkungen | Potenzial |
| Serotonin-antagonisten | Ondansetron | 8 mg i.v., 2 x 4-8 mg p.o. | Kopfschmerzen, Diarrhoe, Flushsymptomatik Transaminasenanstieg Darmatonie in hoher Dosierung | sehr hoch |
| | Tropisetron Granisetron Palonosetron | 5 mg i.v., 5 mg p.o. 1-3 mg i.v. 0, 25 mg i.v. | | |
| NK1-Antagonisten | Aprepitant | 125 mg d1, 80 mg d 2-3 p.o. | Cytochrom-P-450- Aktivierung mit Dosis-reduktion von Dexamethason (2 x 8 mg). Keine Kombination mit Astemizol, Terfenadin, Cisaprid | sehr hoch |
| | Fosaprepitant Rolapitant | 150 mg d1 i.v. 180 mg d1 p.o. | | |
| Dopamin-antagonisten/ substituierte Benzamide | Metoclopramid | bis zu 120 mg/24h als Dauerinfusion od. als Tropfen | Dyskinesien (Antidot:Biperiden) | hoch |
| | Alizaprid | bis zu 300 mg i.v. oder p.o./24 h (6 Amp. od. 6 Tbl.) | | |
| Oxazapine | Olanzapin | 10mg/d for d1-4 Ggf. 5mg/d for d1-4 | Sedation, Gewichtszunahme | hoch |
| Phenothiazine/ Butyrophenone | Haloperidol | 1-3 mg 4 x/d | Sedation, Senkung der Krampfschwelle, transiente Leberwerterhöhung | mäßig |
| Corticosteroide | Dexamethason | 8-20 mg i.v. 1-3 x/d | Blutzuckerentgleisung, psychotische Reaktionen, Flush, Blutdruckanstieg | mäßig |
| | Prednisolon | 100-250 mg i.v. 1-3 x/d | | |
| Benzodiazepine | Diazepam Lorazepam | bis zu 20 mg/d 0,5-1,0 mg/d | Sedation, Atemdepression | gering |
| NEPA (Netupitant and Palonosetron) | fixe Kombinations partner (oral) | NE 300 mg PA 0,5 mg | | sehr hoch |



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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, 2019DOI:[https://doi.org/10.1016/S1470-2045\(19\)30678-3](https://doi.org/10.1016/S1470-2045(19)30678-3)
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Mukositis Prävention

[http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006\(dtV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006(dtV).pdf)
Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL): „Supportive Therapie bei onkologischen Patientinnen – interdisziplinäre Querschnittsleitlinie“, released 11.11.2016

| | Oxford | | |
|---|--------|----|-----|
| | LoE | GR | AGO |
| <ul style="list-style-type: none"> Standardisierte Mundpflege zur Prophylaxe oraler Mukositis soll in allen Altersgruppen und bei allen Krebsbehandlungen mit einem Risiko für OM erfolgen | 2b | | ++ |

Diese besteht aus

1. Patientinnenseitig
 - regelmässige Mundspülung (H₂O, NaCl)
 - Weiche Zahnbürste
 - Reinigung der Zahnzwischenräume mit Zahnseide und/oder Interdentalbürsten
 - Vermeidung von Noxen (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: Allopurinol, Capsaicin, Glutamin, Honig, Kamille, Kamillosan, Kaugummi, Kefir, Methadon, Nystatin, Pentoxiphyllin, Polividon Jod, Vitamine A/E/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)

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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 NRF 7.14.)

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

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Mukositis

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

- **Desinfizierende / entzündungshemmende Maßnahmen:**
Mundspülung mit Kamille- oder Salbeitee bzw. Kamillenextrakt, äther. Öle, Iod-Polyvidon, Hexetidin.
Pinselfungen mit Kristallviolettlösung 0,5% (Rezeptur) oder Myrrhentinktur, H. Mometasonfuroat + Propylenglykol
- **Schleimhautschützende Maßnahmen (während / nach Zytostatikaapplikation):**
Lutschen von Eiswürfeln (bes. geeignet: Ananassaft, über die Apotheke beziehbar) während 5-Fluorouracil- oder HD-Melphalan-Infusion. Calciumfolinat (Leucovorin-Mundgel®, H) bei HD-Methotrexat: frühestens 24 Stunden nach Ende MTX-Infusion beginnen (sonst Wirkungsverlust des Zytostatikums!), 4- bis 6-stündlich.
Dexpantenol (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:** Opiode 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)
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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.



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Diarrhoe

- **Adsorbantien**
 - Carbo medicinalis, Kaolin / Pektin, Al-Mg-Silikathydrat
- **Analgetica, Opioide**
 - Loperamid Codein , Morphin i.v. , Tinktura opii, Butylscopolamin
- **Pseudomembranöse Kolitis**
 - Metronidazol oder bei Versagen Vancomycin


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.
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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.
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6. 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.
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Obstipation


Wichtige Nebenwirkung einer Opiattherapie

- **Quellmittel**
 - Flohsamen, 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,

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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,

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



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GYNAKOLOGISCHE
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Hauttoxizität

| | Oxford | | |
|---|--------|----|-----|
| | LoE | GR | AGO |
| ▪ Vermeidung einer ausgeprägten chemotherapie-induzierten Alopezie durch Kopfhautkühlung* | 1b | | +/- |
| ▪ Eine Prophylaxe des HFS mit harnstoffhaltigen 5–10% Cremes kann erfolgen (mehrfach tägl.) | 1b | | + |
| ▪ Unter Docetaxel sollte eine Prophylaxe der Nagelveränderungen/HFS durch Kühlung erfolgen | 2b | | + |

* 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.



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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)

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.



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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,

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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,

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

| | Oxford | | |
|---|-----------|----------|-----------|
| | LoE | GR | AGO |
| ▪ Dexrazoxane zur Behandlung von Anthracyclin-Paravasaten (Ausnahme liposomales A) | 2b | B | ++ |
| ▪ Hyaluronsäure zur Behandlung von Taxan/Vinorelbin-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 1.2, 2019, AWMF Registernummer: 032/054OL, <http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html> (Zugriff am 08.01.2020)

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 Anthrazyklin-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-stündlich 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/Vinorelbin-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)

■ Substanzspezifische Nebenwirkungen

- Antikörper und Antikörper-Wirkstoff-Konjugate (ADC)
- CDK 4/6-Inhibitoren
- PARP-Inhibitoren
- Small molecules (TKI, mTOR-Inhibitor)
- Immun-Checkpoint-Antikörper
- PI3-Kinase-Inhibitoren (Alpelisib)



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Nebenwirkungen – Antikörper/ Antikörper-Wirkstoff-Konjugate

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



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Toxizitäten neuer Substanzen – CDK 4/6 Inhibitoren (Palbociclib / Ribociclib / Abemaciclib)

| UE, % | Alle Grade | Grad 3 | Grad 4 |
|---|--------------------------|----------------------------------|--------------------------------|
| Neutropenie | 79,5/ 74,3 /41,3 | 56,1/ 49,7 /19,6 | 10,4/ 9,6 /1,5 |
| Leukopenie | 39,0/ 32,9 /20,8 | 24,1/ 19,8 /7,3 | 0,7/ 1,2 /0,3 |
| Anämie | 24,1/ 18,6 /28,4 | 5,2/ 0,9 /5,8 | 0,2/ 0,3 /0 |
| Thrombopenie | 15,5/ 5,7 /10,0 | 1,4/ 0,6 /2,0 | 0,2/ 0 / <1,0 |
| Fatigue | 37,4/ 36,5 /40,1 | 1,8/ 2,1 /1,8 | 0/ 0,3 /0 |
| Übelkeit | 35,1/ 51,5 /38,5 | 0,2/ 2,4 /0,9 | 0/ 0 /0 |
| Erbrechen | 15,5/ 29,3 /28,4 | 0,5/ 3,6 /1,2 | 0/ 0 /0 |
| Diarrhoe | 26,1/ 35,0 /81,3 | 1,4/ 1,2 /9,5 | 0/ 0 /0 |
| Alopezie | 32,9/ 33,2 /26,6 | - | - |
| Exanthem | 17,8/ 17,1 / 14,0 | 0,9/ 0,6 / <1,0 | 0/ 0 /0 |
| ALT Erhöhung | 9,9/ 15,6 /15,6 | 1,7/ 7,5 /5,8 | 0,1/ 1,8 /0,3 |
| AST Erhöhung | 9,7/ 15,0 /15,0 | 2,5/ 4,8 /3,0 | 0/ 0,9 /0 |
| Infektionen | 60/ 50,3 /39,1 | 6,0/ 3,6 /4,0 | 1/ 0,6 /0,9 |
| QT Prolongation | N.A./ 7,5 /N.A. | N.A./ 3,0 /N.A. | N.A./ 0 /N.A. |
| Palbociclib/ Ribociclib /Abemaciclib | | | |

Palbociclib


1. 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.
2. N.Harbeck, J. Ettl, Palbociclib, CDK 4/ 6 Inhibition als neue Therapieoption bei Patientinnen mit fortgeschrittenem HR+/ Her – Mammakarzinom. Drug Report, 2017

Ribociclib

1. 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

1. 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.
2. 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.



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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.

| <div>  Toxizitäten neuer Substanzen: mTOR-Inhibitor (Everolimus) </div> | | | |
|---|------------------|----------------|--------------|
| <div>  <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p> </div> | UE, % | Alle Grade (%) | Grad >=3 (%) |
| | Stomatitis | 11,6 | 1,6 |
| | Ausschlag | 7,4 | 0,02 |
| | Anämie | 3,3 | 1,3 |
| | Fatigue | 6,8 | 0,8 |
| | Übelkeit | 5,6 | 0 |
| | Erbrechen | 2,9 | 0 |
| | Diarrhoe | 6,2 | 0,02 |
| | Appetitminderung | 6,0 | 0,02 |
| | Kopfschmerz | 3,9 | 0 |
| | Gewichtsverlust | 3,9 | 0 |
| | Dyspnoe | 3,8 | 0,08 |
| | Arthralgie | 3,3 | 0 |
| | Epistaxis | 3,1 | 0 |
| | Ödem | 2,9 | 0 |
| | Obstipation | 2,6 | |
| | Pyrexie | 2,9 | 0 |
| | Husten | 4,5 | 0 |
| | ALT Erhöhung | 2,6 | 0 |
| | Pneumonitis | 0,2 | 0 |
| | Asthenie | 2,4 | 0,04 |
| | 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



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Toxizitäten PARP-Inhibitoren – Olaparib, Talazoparib

Olaparib

| UE, % | Alle Grade (%) | Grad >=3 (%) |
|------------------|----------------|--------------|
| Jegliche UE | 97,1 | 36,6 |
| Neutropenie | 27,3 | 9,3 |
| Anämie | 40,0 | 16,1 |
| Fatigue | 28,8 | 2,9 |
| Übelkeit | 58,0 | 0 |
| Erbrechen | 29,8 | 0 |
| Diarrhoe | 20,5 | 0,5 |
| Appetitminderung | 16,1 | 0 |
| Kopfschmerz | 20,0 | 1 |
| Pyrexie | 14,1 | 0 |
| Husten | 17,1 | 0 |
| ALT Erhöhung | 11,2 | 1,5 |
| AST Erhöhung | 9,3 | 2,4 |
| PPE | 0,5 | |
| Therapieabbruch | 4,9 | |

Talazoparib

| UE, % | Alle Grade (%) | Grad >=3 (%) |
|------------------|----------------|--------------|
| Jegliche UE | 98,6 | 31,8 |
| Neutropenie | 34,6 | 20,9 |
| Anämie | 52,8 | 39,2 |
| Fatigue | 50,3 | 1,7 |
| Übelkeit | 48,6 | 0,3 |
| Erbrechen | 24,8 | 2,4 |
| Diarrhoe | 22,0 | 0,7 |
| Appetitminderung | 21,3 | 0,3 |
| Kopfschmerz | 32,5 | 1,7 |
| Pyrexie | 21,0 | 2,4 |
| Husten | 17,5 | 2,4 |
| ALT Erhöhung | 2,1 | 1,7 |
| AST Erhöhung | 1,4 | 0,3 |
| PPE | 98,6 | 31,8 |
| Therapieabbruch | 34,6 | 20,9 |

1. Litton JK, Rugo 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

Toxizitäten antiHER2-TKI – Neratinib, Lapatinib –

Lapatinib


| UE, % | Alle Grade | Grad >=3 |
|------------------|------------|----------|
| Diarrhöe | 61% | 6% |
| Nausea | 18% | 4% |
| Hautausschlag | 60% | 6% |
| Fatigue | 16% | 4% |
| Kardiale NW | 3% | < 1% SAE |
| Hepatobiliäre NW | 8% | |
| Alle UE | 92% | SAE 6% |

Neratinib

| UE, % | Alle Grade (%) | Grad >=3 (%) |
|-----------------|----------------|--------------|
| Diarrhöe | 90 | 40,1 |
| Nausea | 43 | 2 |
| Bauchschmerzen | 36 | 2 |
| Fatigue | 27 | 2 |
| Erbrechen | 26 | 3 |
| Hautausschlag | 18 | 0,6 |
| Stomatitis | 14 | 0,6 |
| Appetitverlust | 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 AGO
2b B ++

1. Chan A, Delagoge S, Holmes FA et al Neratinib after trastuzumab –based adjuvant therapy in patients with HER2 positive breast cancer (ExteNET): a multicentr, randomized, double.-blind, placebo controlled , phase III trial. Lancet Oncol 17(39: 367-377, 2016
2. 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
3. Neratinib: FDA Produktinformation 2017



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Nebenwirkungen PIK3CA in Kombination mit endokriner Therapie

Alpelisib+Fulvestrant

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

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


LoE
2b

AGO
B

AGO
++

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.



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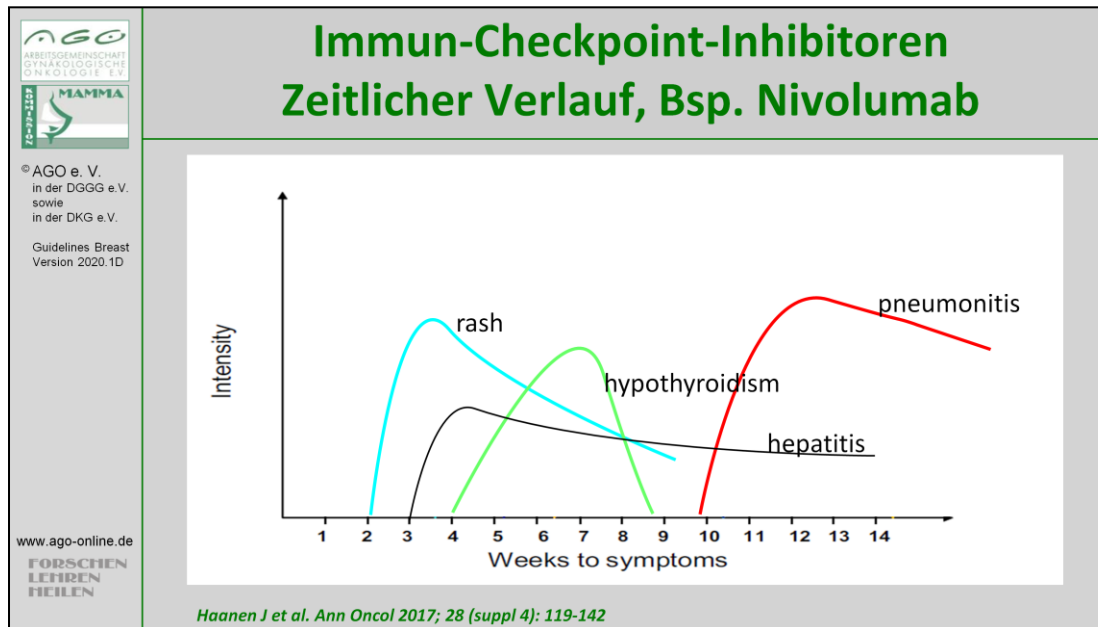
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Immun-Checkpoint-Inhibitoren

- **Therapeutische Ansätze (Antikörper)**
 - **PD1 /PD-L1**
 - PD1**
 - Nivolumab
 - Pembrolizumab
 - PDL1**
 - Atezolizumab
 - Durvalumab
 - Avelumab

1. Haanen J, Carbone 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. doi: 10.1093/annonc/mdx225
2. Ingrid A. Mayer¹, Aleix Prat², Daniel Egle³, et al.: A Phase II Randomized Study of Neoadjuvant Letrozole Plus Apolisib 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, Carbone 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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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, Carbone 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% |
| Schilddrüsen- 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

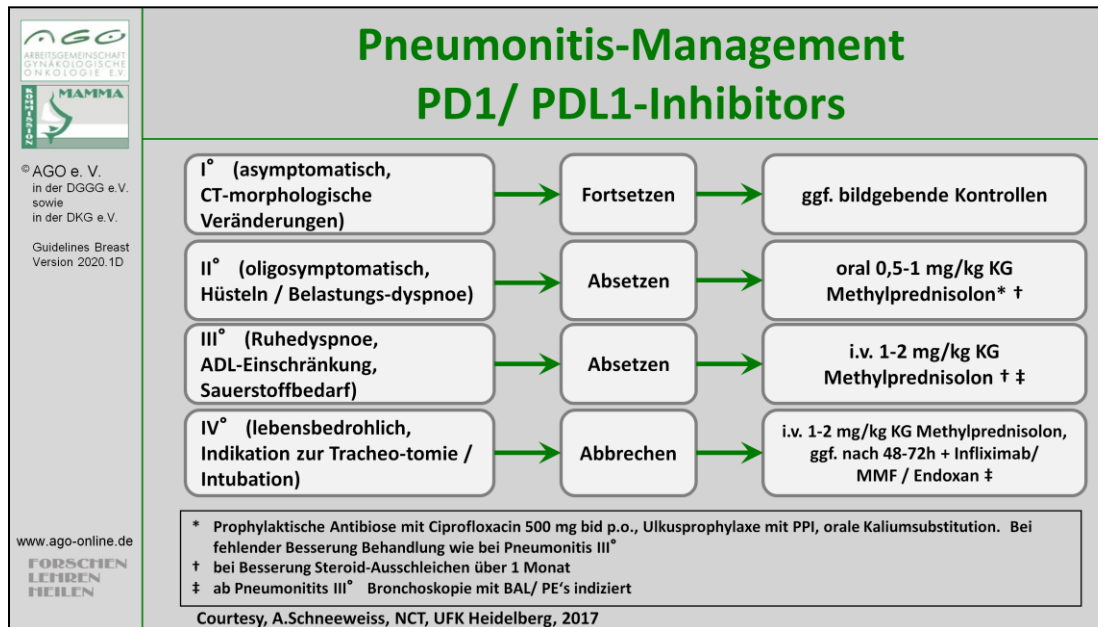
Atezolizumab: <https://www.fachinfo.de/suche/fi/021700>

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

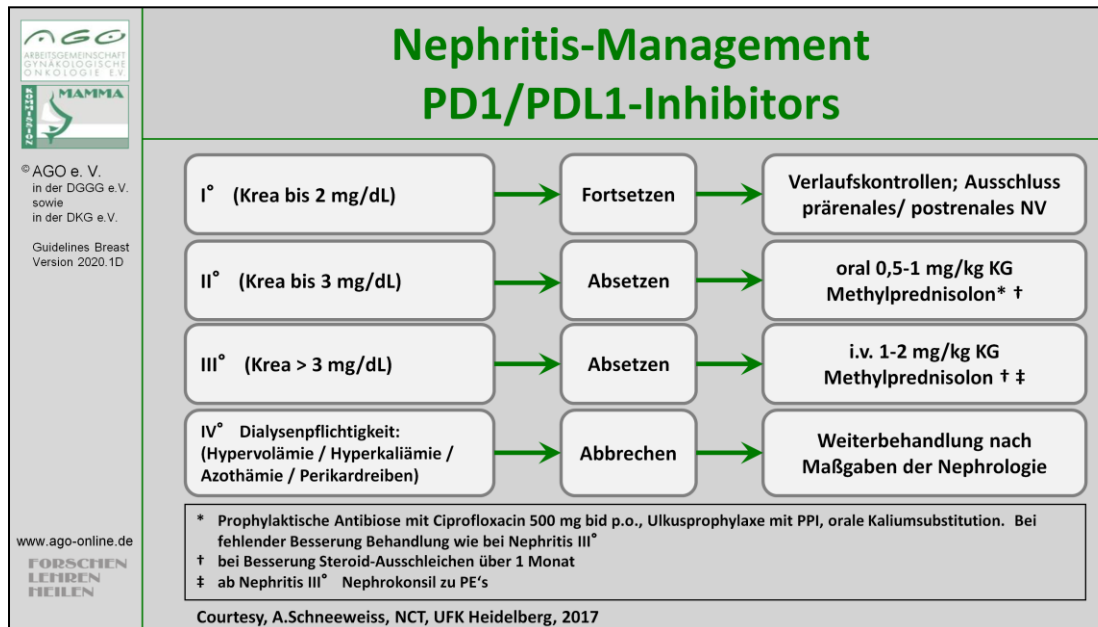
Pembrolizumab: <https://www.fachinfo.de/suche/fi/020716>

|  <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2020.1D</p> <p>www.ago-online.de</p>  | <h2 style="text-align: center;">Immun-Checkpoint-Inhibitoren NW-Management - Grundsätze</h2> <table border="1"> <thead> <tr> <th>CTC AE-Grad</th><th>Management</th></tr> </thead> <tbody> <tr> <td>1</td><td> <ul style="list-style-type: none"> Supportive Therapie Engmaschige Kontrollen Ausschluss Infektion Patientenaufklärung </td></tr> <tr> <td>2</td><td> Wie Grad 1 aber <ul style="list-style-type: none"> Pausierung der Therapie bis alle irAE Grad 0-1 Ggf Kortikosteroide </td></tr> <tr> <td>3</td><td> <ul style="list-style-type: none"> Supportive Therapie i. v.-Steroide (z. B. 1-2 mg/kg Prednisolon) Wenn keine Besserung innerhalb 48 h: <ul style="list-style-type: none"> Ggf zusätzliche andere Immunsuppression (Infliximab, 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 Langsames Ausschleichen der Steroide (3-6 Wochen) </td></tr> <tr> <td>4</td><td>Wie Grad 3 aber dauerhaftes Absetzen der Therapie</td></tr> </tbody> </table> | CTC AE-Grad | Management | 1 | <ul style="list-style-type: none"> Supportive Therapie Engmaschige Kontrollen Ausschluss Infektion Patientenaufklärung | 2 | Wie Grad 1 aber <ul style="list-style-type: none"> Pausierung der Therapie bis alle irAE Grad 0-1 Ggf Kortikosteroide | 3 | <ul style="list-style-type: none"> Supportive Therapie i. v.-Steroide (z. B. 1-2 mg/kg Prednisolon) Wenn keine Besserung innerhalb 48 h: <ul style="list-style-type: none"> Ggf zusätzliche andere Immunsuppression (Infliximab, 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 Langsames Ausschleichen der Steroide (3-6 Wochen) | 4 | Wie Grad 3 aber dauerhaftes Absetzen der Therapie |
|--|--|-------------|------------|---|--|---|---|---|--|---|---|
| CTC AE-Grad | Management | | | | | | | | | | |
| 1 | <ul style="list-style-type: none"> Supportive Therapie Engmaschige Kontrollen Ausschluss Infektion Patientenaufklärung | | | | | | | | | | |
| 2 | Wie Grad 1 aber <ul style="list-style-type: none"> Pausierung der Therapie bis alle irAE Grad 0-1 Ggf Kortikosteroide | | | | | | | | | | |
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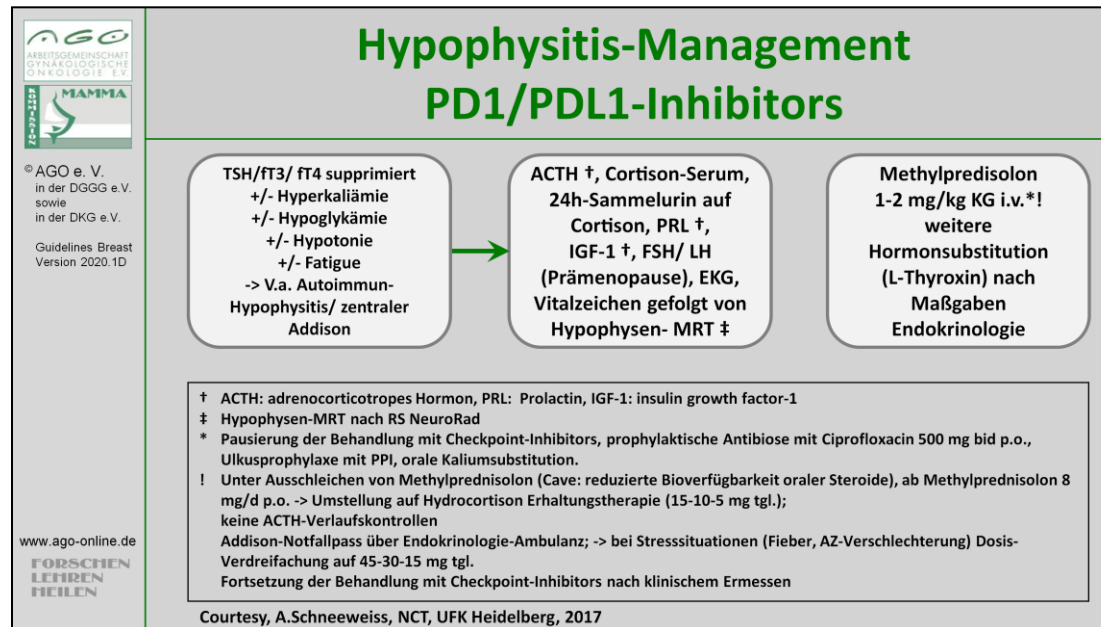
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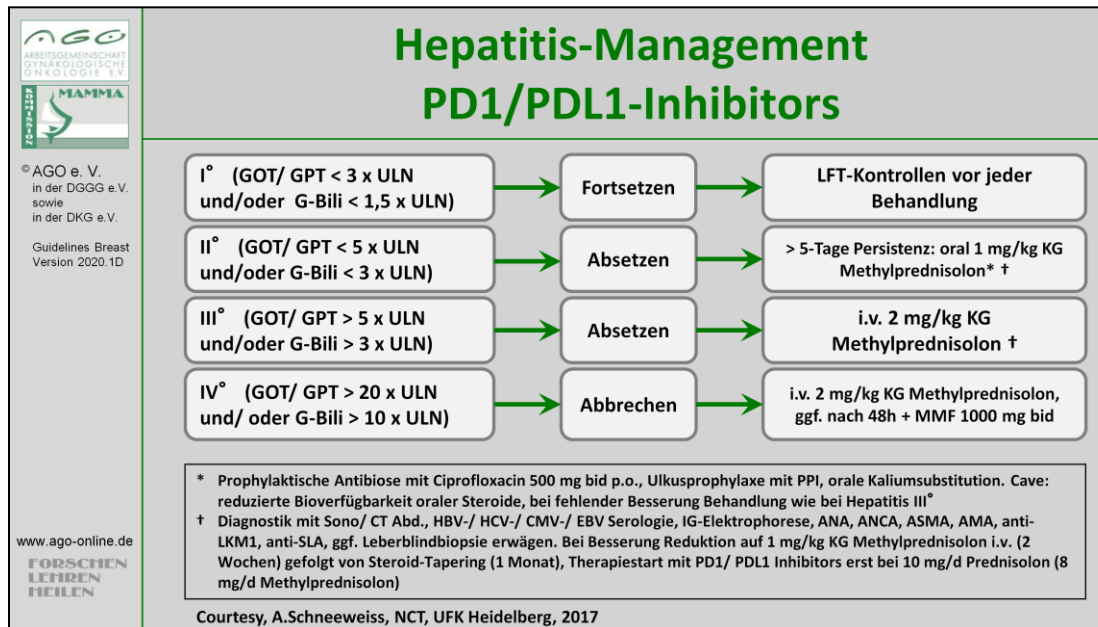
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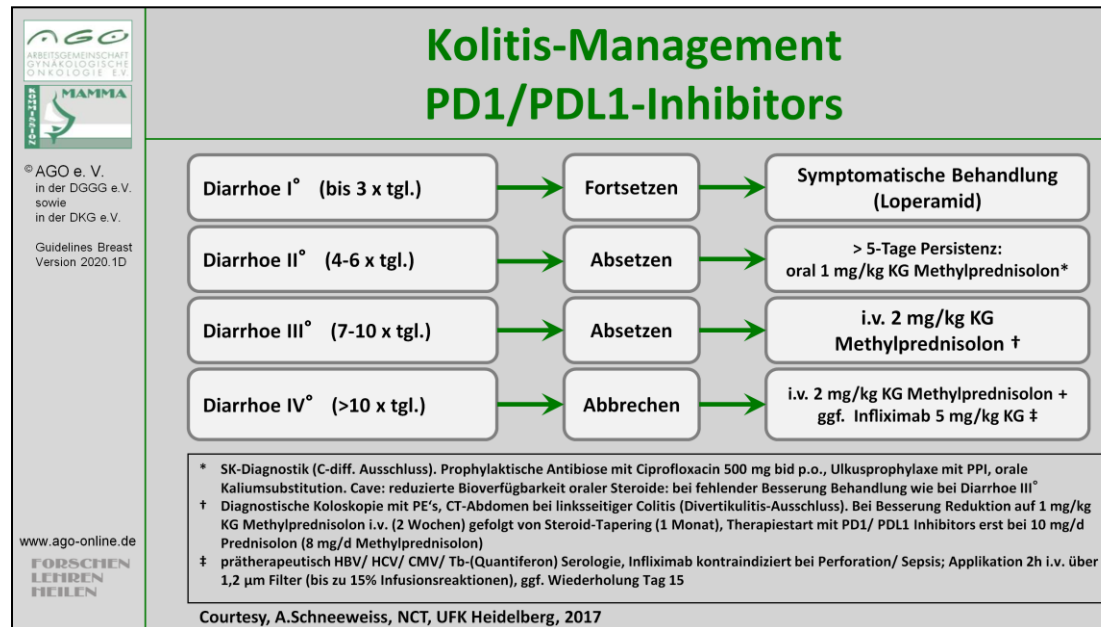
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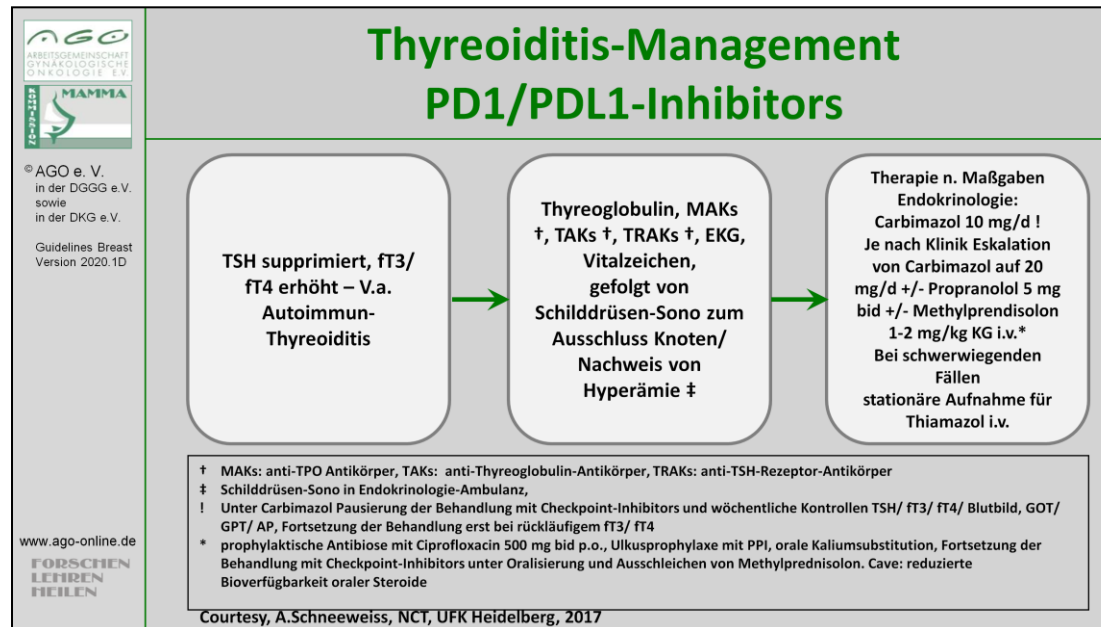
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2. Postow M, Sidlow R, Hellmann M: Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018; 378(2): 158-168. doi: 10.1056/NEJMra1703481

■ Andere supportive und palliative Fragestellungen

- Ernährung
- Schmerztherapie
- Palliative Care



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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 Ernährungsmed 2015; 40: e1–e74 www.awmf.org/uploads/tx_szleitlinien/073-0061_S3_Klin_Ernährung_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 MMGA](#)¹, [Kok DE](#)², [Posthuma L](#)¹, et al [Breast Cancer Res Treat](#). 2019 Jan;173(2):475-481. doi: 10.1007/s10549-018-5014-5. Epub 2018 Oct 23.



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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), Hydromorphon, Oxycodon, als Reserve Levomethadon. Die notwendige Opioiddosis 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:

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



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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)