Supportive Care and Management of Side Effects

Screened data bases

Screened guidelines
Supportive Care and Management of Side Effects

- **Versions 2002–2022:**

- **Version 2023:**
  Maass / Park-Simon
Guidelines – Evidence

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

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

Aspects concerning breast cancer patients will especially be highlighted.

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

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

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

1. **S3-Leitlinie Supportive Therapie:**
   https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Supportivtherapie/LL_Supportiv_Langversion_1.3.pdf

2. **ESMO Clinical Practice Guidelines: Supportive and Palliative Care.** www.esmo.org


Toxicity Assessment

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

Acute Toxicity (according to WHO¹ or NCI-CTC²)

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

LoE 5 D AGO ++

<table>
<thead>
<tr>
<th>Grade</th>
<th>Information required</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>none organs involved</td>
</tr>
<tr>
<td>1</td>
<td>mild type of toxicity</td>
</tr>
<tr>
<td>2</td>
<td>moderate time interval after treatment</td>
</tr>
<tr>
<td>3</td>
<td>severe effect on general health status</td>
</tr>
<tr>
<td>4</td>
<td>life threatening treatment required</td>
</tr>
<tr>
<td>5</td>
<td>death recovery achieved</td>
</tr>
</tbody>
</table>

Long term Toxicity (= secondary diseases after tumour therapy)

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

LoE 5 D AGO ++

Acute Toxizität
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

Langzeittoxizität
3. Kenyon M, Mayer DK, Owens AK. Late and long-term effects of breast cancer treatment and surveillance management for the general


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)
Incidence of Side Effects

- According to product information by MedDRA* classification

*MedDRA - Medical Dictionary for Regulatory Activities

https://www.meddra.org/
Listing and grading of side effects was performed according the MedDRA classification with the following categories of frequency:

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

- unknown (based on available data incidence not assessable)
fachinformation
9. Doxorubicin:
fachinformation
fachinformation
fachinformation
13. Paclitaxel: https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil
fachinformation
15. Docetaxel: https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d

Further references (selection)


10. Crawford J.


Chemotherapy – Acute Toxicities II

### Abbreviations
AML = Acute myeloid Leucemia; DPD = Dihydropyrimidin-Dehydrogenase; CHF = congestive heart failure; CIPN = Chemotherapy-induced peripheral neuropathy; HFS = Hand-Foot-Syndrom; PPE = Palmar and plantar Erythema

### Side effect categories - MedDRA (Medical Dictionary for Regulatory Activities)
   https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf

### Sources for product information (Download 19.01.2018)
2. Methotrexat: https://www.gelbe-liste.de/produkte/MTX-HEXAL-10-mg-Tabletten_117469/fachinformation
3. 5-Fluorouracil: https://www.gelbe-liste.de/produkte/Fluorouracil-HEXAL-50-mg-ml-Injektionsloesung-100-ml_546519/fachinformation
4. Capecitabin: https://www.zentiva.de/Produkte/Capecitabin-Zentiva/Downloads?id=a63946ee-51ce-46ac-8184-a468b705ed9b

---

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

1. Very rarely (<1/10,000);
2. Rarely (≥ 1/1,000 to < 1/10,000);
3. Occasionally (≥ 1/1,000 to < 1/100);
4. Frequently (≥ 1/100 to < 1/10);
5. Very frequently (≥ 1/10).
7. Carboplatin: http://www.teva.de/index.php?eID=1&r=11068%2C11068&token=eebfb22e78f1cc8d9935d59c087e80630146f49e
8. Epirubicin:
9. Doxorubicin:
13. Paclitaxel: https://medikamio.com/de-de/medikamente/paclitaxel-ratiopharm/pil
15. Docetaxel: https://mein.sanofi.de/produkte/Taxotere/Downloads?id=89447754-dfb2-450b-b35a-36950de8a74d

Further references (selection)
Onkologie 36(5): 266-272.


10. Crawford J.


Diagnostics* before Start of 5-FU (i.v.) / Capecitabine-Therapy

- **DPD (Dihydropyrimidin-Dehydrogenase) - Deficiency** Testing (DPYD-Genotype or Phenotype)
  - Phenotype determination (e.g. uracil in plasma / urine, determination of DPD-activity) are less standardized assays
  - **Systematic review (cancer patients under 5-FU therapy)**:
    - DPYD-variants (heterozygous or homozygous) 4.1%
    - Therapy-associated mortality 2.3% (vs. 0.1% w/o DPYD-variants) – risk for therapy-associated death 25.6-fold increase

**Recommendation according to Medical Alert (Rote-Hand-Brief) 4.6.2020**

**Sharma et al, Oncologist 2021**

**DPD Deficiency:**
1. Rote-Hand-Brief vom 04.06.2020: https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RHB/2020/rhb-fluorouracil.html (Zugriff am 17.01.2022)
Endocrine Therapy – Toxicities

Side effect categories- MedDRA (Medical Dictionary for Regulatory Activities)

Sources for product information (Download 19.01.2018)
1. Tamoxifen: https://www.gelbe-liste.de/produkte/Tamoxifen-20-mg-HEXAL-Filmtabletten_8660/fachinformation
2. Anastrozol: https://imedikament.de/anastrozol-ratiopharm-1-mg-filmtabletten/fachinformation

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

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

- unknown (based on available data incidence not assessable)
Key-Toxicities – Antibodies

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>• Cardiotoxicity in the adjuvant setting (1.0–2.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Troponin I may identify patients at risk for cardiotoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>• Skin rash, diarrhea, mucositis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>• Hypertension, proteinuria, bleeding, left ventricular dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

Cardiotoxicity


Troponin I

Pertuzumab

Bevacizumab ....
Common Toxicities with anti-HER2-TKI: Tucatinib + Trastuzumab + Capecitabine

<table>
<thead>
<tr>
<th>Event</th>
<th>Capecitabine + Tucatinib + Trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade (%)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>99.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>80.9</td>
</tr>
<tr>
<td>PPE syndrome</td>
<td>63.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>58.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>35.9</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>25.5</td>
</tr>
<tr>
<td>Reduced appetite</td>
<td>24.8</td>
</tr>
<tr>
<td>Headache</td>
<td>21.5</td>
</tr>
</tbody>
</table>

2. Tucatinib, Trastuzumab, Capecitabin s. aktuelle Fachinformation www. Fachinfo.de
Key-Toxicities – Antibody-Drug-Conjugates

Sacituzumab Govitecan
- (Febrile) neutropenia, leukopenia, anemia, diarrhea, nausea, alopecia
- Thrombocytopenia, elevation liver enzymes, pyrexia, headache
- Interstitial lung disease, neuropenia, nausea, alopecia,

Trastuzumab-Emtansin (T-DM1)
- Thrombocytopenia, elevation liver enzymes, pyrexia, headache

Trastuzumab-Deruxtecan
- Interstitial lung disease, neuropenia, nausea, alopecia,

Oxford
LoE GR

Sacituzumab Govitecan


T-DM1


Palbociclib
Ribociclib

Abemaciclib
Interstitial Lung Disease (ILD) and CDK 4/6 Inhibitors

Pulmonary toxicity of cyclin-dependent kinase (CDK) 4/6 inhibitors from the publicly available FDA Adverse Event Reporting System (FAERS):
- 2.1% of all reports for abemaciclib; 0.3% of all reports palbociclib / ribociclib
- Increased reporting found for
  - CDK4/6 inhibitors vs. other drugs (ROR = 1.50; 95% CI = 1.28–1.74)
  - Abemaciclib vs other anticancer agents (4.70; 3.62–5.98).

Overall incidence:
Systematic review of published data:
CDK 4/6i: Any grade 1.64% (0.68% control). Pooled RR 2.26. 95% CI: 1.60-3.19, p < 0.00001
CDK 4/6i: Grade 3/4 0.28% (0.06% control). Pooled RR 2.35, 95% CI: 0.37-15.08, p = 0.37

Monarch-E:
Abemaciclib any grade 2.9% (> G3 0.4% - 1 G5 event); control 1.2% (> G3 n = 1; 0%)

2. Toi M, Harbeck N, Puig JM et al. Characterization of venous thromboembolic events (VTE), elevated aminotransferases (EAT) and interstitial lung disease (ILD) in monarchE. ESMO Breast 2021

2. Toi M, Harbeck N, Puig JM et al. Characterization of venous thromboembolic events (VTE), elevated aminotransferases (EAT) and interstitial lung disease (ILD) in monarchE. ESMO Breast 2021
### Toxicities of mTOR-Inhibitor (Everolimus)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>All grades (%)</th>
<th>grade &gt;/=3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomatitis</td>
<td>11.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Exanthema</td>
<td>7.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.6</td>
<td>0</td>
</tr>
<tr>
<td>Nausea / Vomiting</td>
<td>2.9</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>6.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Headache</td>
<td>3.8</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3.9</td>
<td>0</td>
</tr>
<tr>
<td>Syncope</td>
<td>3.8</td>
<td>0.08</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.3</td>
<td>0</td>
</tr>
<tr>
<td>Epigastralgia</td>
<td>2.1</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>2.9</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.6</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2.9</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>4.8</td>
<td>0</td>
</tr>
<tr>
<td>ALT Elevated</td>
<td>2.8</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>4.3</td>
<td>0</td>
</tr>
</tbody>
</table>

Toxicities of PI3K Inhibitor Alpelisib in Combination with Endocrine Therapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>All Grade</th>
<th>Grad ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypergycemia</td>
<td>63.7%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57.7%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>44.7%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>35.6%</td>
<td>&lt;1% SAE</td>
</tr>
<tr>
<td>Rash</td>
<td>35.5%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27.1%</td>
<td>&lt;1% SAE</td>
</tr>
<tr>
<td>Weight loss</td>
<td>26.8%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>24.6%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24.3%</td>
<td>3.5</td>
</tr>
<tr>
<td>Asthenia</td>
<td>20.4%</td>
<td>1.8</td>
</tr>
<tr>
<td>Alopecia</td>
<td>19.7%</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>18.3%</td>
<td>2.1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
</tbody>
</table>


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

Immune Checkpoint Inhibitors

- **Therapeutic approaches (antibodies)**
  - PD-1 / PD-L1
    - PD-1
      - Nivolumab
      - Pembrolizumab
    - PD-L1
      - Atezolizumab
      - Durvalumab
      - Avelumab

Immune Checkpoint Inhibitors
– Side Effects –

- **Adverse events ≥ grade 3**
  - diarrhea
  - fatigue
  - skin lesions (maculopapular exanthema, vitiligo, epidermolysis)
  - pneumonitis
  - colitis
  - hypophysitis
  - hepatitis
  - nephritis
  - thyreoiditis (hyper- / hypothyroidism)
  - Guillain-Barré syndrome
  - cardiomyopathy
  - myopathy – myalgia – rhabdomyolysis
  - uveitis

Immune Checkpoint Inhibitors
Toxicities (Total in %)

<table>
<thead>
<tr>
<th></th>
<th>atezolizumab</th>
<th>nivolumab</th>
<th>pembrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>diarrhea</td>
<td>18.6%</td>
<td>13%</td>
<td>18%</td>
</tr>
<tr>
<td>colitis</td>
<td>1.1%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>exanthema</td>
<td>18.6%</td>
<td>15%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>hepatitis</td>
<td>0.3%</td>
<td>1%</td>
<td>0.5%</td>
</tr>
<tr>
<td>hypophysis</td>
<td>&lt; 0.1%</td>
<td>&lt; 1%</td>
<td>0.5%</td>
</tr>
<tr>
<td>pneumonia</td>
<td>3.1%</td>
<td>3%</td>
<td>2.9%</td>
</tr>
<tr>
<td>thyroid dysfunction</td>
<td>hyper-1.7%</td>
<td>hyper-1%</td>
<td>hyper-1.2%</td>
</tr>
<tr>
<td></td>
<td>hypo-4.7%</td>
<td>hypo-4%</td>
<td>hypo-8.3%</td>
</tr>
<tr>
<td>nephritis</td>
<td>&lt; 1%</td>
<td>1%</td>
<td>0.7%</td>
</tr>
<tr>
<td>neuropathy</td>
<td>0.2%</td>
<td>&lt; 1%</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

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

1. Atezolizumab: https://www.fachinfo.de/suche/fi/021700
2. Nivolumab: https://www.fachinfo.de/suche/fi/020675
3. Pembrolizumab: https://www.fachinfo.de/suche/fi/020716


### Immune Checkpoint Inhibitors
#### Principles of Adverse Event Management

<table>
<thead>
<tr>
<th>CTC AE-Grade</th>
<th>Management</th>
</tr>
</thead>
</table>
| 1            | • supportive therapy  
• close examination  
• exclusion of infective complications  
• patient information  |
| 2            | Like grade 1 but  
• intermission of therapy until recovery of all irAE to grades 0-1  
• consider corticosteroids  |
| 3            | Like grade 3 but persistent withdrawal of therapy  
• supportive therapy  
• IV steroids (e.g. 1-2 mg/kg prednisolone)  
In case of no improvement within 48 h:  
• consider additional immunosuppressive therapy (infliximab, MMF)  
• consider further organ specific diagnostics (eg. colonoscopy)  
• consider specialists consultations  
• exclusion or treatment of infection  
• stop of treatment, re-initiation after recovery to CTC AE grades 0, 1  
• slow reduction of steroids (3-6 weeks)  |
| 4            | Like grade 3 but persistent withdrawal of therapy  |


Thyreoiditis

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

Prophylaxis of Infections rarely Applicable to Patients with Solid Tumors (e.g. BC)
ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2018

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

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

ASCO:

NCCN:


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### Hepatitis B Virus Screening before Chemotherapy

- **Hepatitis B virus screening before adjuvant chemotherapy (HBsAG, anti-HBC, anti-HBs)**
  - Oxford LoE GR AGO
  - 2c B +

**In case of positive serology or reactivation:**

- **Prophylactic therapy with virustatic drugs if HBV-DNA detected (according AGIHO / DGHO – recommendations)**
  - 1b A ++

- **Hepatitis C virus screening before chemotherapy**
  - 5 D +/-

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

Statements 1-5


Tamoxifen and endometrial cancer


Secondary Malignancies II
(After Radiotherapy)

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


3. Blood and Lymphatic System Disorders
   - Anemia
   - Neutropenia
   - Febrile Neutropenia (FN)
Anemia – Indications for Therapy with Erythropoiesis-stimulating Agents (ESAs)

Leitlinie:
Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020,
AWMF Registernummer: 032/054OL

5. Aapro M, Moebus V, Nitz U et al.: Safety and efficacy outcomes with erythropoiesis-stimulating agents in patients with breast cancer:


Relevante Leitlinien


**Relevant guidelines**

### Relevante Leitlinien

1. **S3-Leitlinie: Supportive Therapie:**
   Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3 – Februar 2020

2. **NCCN Guidelines 1.2022**


### Statements 1-4


2. **Lyman GH, Dale DC, Culakova E et al.:** The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and

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**Granulocyte Colony-Stimulating Factors**

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prophylaxis for expected febrile neutropenia (FN)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If expected risk for FN 10–20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If expected risk for FN &gt; 20% (e.g. DAC, dose-dense CT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>C</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary prophylaxis during chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(previous FN or neutropenia grade IV &gt; 7 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td><strong>Therapeutic use for FN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td><strong>Start related to chemotherapy and duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegfilgrastim day 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipegfilgrastim day 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filgrastim / Lenograstim from day 2–3 until ANC &gt; 2–3 x 10⁹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>


### Management of Febrile Neutropenia

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

#### Definition
(oral temperature of > 38.5°C or two consecutive readings of > 38°C for 2 h in a patient with an ANC of < 500 cells/mm³ or expected to fall to < 500 cells/mm³)

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

S3-Leitlinie: Supportive Therapie:

1. S3-Leitlinie: Supportive Therapie:
   Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3 – Februar 2020
2. NCCN Guidelines 1.2022
EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment

4. Toxicities / Ovaries

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

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

6. Chung C. Risk of ovarian function recovery should be considered when switching from treatment with adjuvant tamoxifen to aromatase inhibitor therapy in women with chemotherapy-induced amenorrhea. CA Cancer J Clin. 2018 Jan;68(1):5-6.
8. Fréour T, Barrière P, Masson D. Anti-müllerian hormone levels and evolution in women of reproductive age with breast cancer


5. Psychiatric Disorders

- Depression
- Fatigue
- Cognitive impairment
- Sleep disturbances
(Therapy-associated) Depression

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

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

Statements 1-4


**Fatigue**

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

**Guideline:**


2. S3-Leitlinie: Supportive Therapie:Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3 – Februar 2020


---

**Fatigue is frequently present...**


Psycho-social interventions...

Physical exercise....


Methylphenidate...


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

Methylphenidate kann kognitive Funktion bei Patientinnen mit Krebs verbessern

Unter Aromatasehemmertherapie wurden kognitive Störungen beobachtet


(Therapy-associated)
Sleep Disturbances

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

- **Behavioral therapies demonstrated efficacy in treatment of insomnia and improved quality of life**
  - 1b A ++

---

Sleep disturbances are a common problem...


Behavioral therapies have demonstrated efficacy.....
6. Nervous system disorders
   - Chemotherapy-Induced Peripheral Neuropathy (CIPN)
Chemotherapy-Induced Peripheral Neuropathy (CIPN)

- **Incidence with taxanes:**
  - Grade 1–2: 20–50%
  - Grade 3–4: 6–20%

- **Risk factors: type and dose of chemotherapy, BMI, reduced physical activity**

- **Individual risk factors**
  - Diabetes mellitus
  - Nutritive-toxic compounds part. alcohol
  - Renal failure
  - Hypothyrosis
  - Collagenoses / vasculitis
  - Vitamine deficiency
  - HIV-Infection
  - CMT-Gen mutations

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

Chemotherapy-induced Peripheral Neuropathy
– Prevention –

Non drug-based prevention

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

Drug-based prevention

There is no drug-based prophylaxis available

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

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

Reviews/Leitlinien


**Nicht-medikamentöse Prävention**

**Funktionstraining**


**Kompression**


Akupunktur


Medikamentöse Prävention

Venlafaxin


Palmitoylethanolamid (PEA)


**Verschiedene Substanzen**


**Acetyl-L-Carnitine**


Chemotherapy-induced Peripheral Neuropathy
– Therapy –

<table>
<thead>
<tr>
<th>Non drug-based therapy</th>
<th>Oxford</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Functional training (physical fitness, sensomotoric stimulation training etc.)</td>
<td>2a C</td>
</tr>
<tr>
<td>• Physiotherapy / physical treatment</td>
<td>5 D</td>
</tr>
<tr>
<td>• acupuncture</td>
<td>2b B</td>
</tr>
<tr>
<td>Drug-based therapy</td>
<td></td>
</tr>
<tr>
<td>• Menthol locally (1%), capsaicin / lidocain locally</td>
<td>5 D</td>
</tr>
<tr>
<td>• Baclofen / amitryptiline / ketamin-gel</td>
<td>2b B</td>
</tr>
<tr>
<td>• Duloxetine for therapy of CIPN-induced pain</td>
<td>1b B</td>
</tr>
<tr>
<td>• Opioids for therapy of CIPN-induced pain</td>
<td>5 D</td>
</tr>
<tr>
<td>• Palmitoylethanolamine (PEA) topically or PO.</td>
<td>5 D</td>
</tr>
<tr>
<td>• Venlafaxine</td>
<td>5 D</td>
</tr>
<tr>
<td>• Gabapentin, pregabalin</td>
<td>1b B</td>
</tr>
<tr>
<td>• Amitryptiline / nortripyline, imipramine / desipramine</td>
<td>1b B</td>
</tr>
</tbody>
</table>
| • Acetyl-L-carnitine, lamotrigine, or other compounds
  For list of not recommended drugs, see Hershman et al. 2014 | 1b B   |

Reviews / Leitlinien


Nicht-medikamentöse Therapie
Funktionstraining

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


Baclofen/Amitryptilin/Ketamin-Creme


Duloxetine


Akupunktur:


Palmitoylethanolamid (PEA)


**Venlafaxin**


**Gabapentin, Pregabalin:**


**Amitriptyline/Nortriptylin**


**Acetyl-L-Carnitin, Lamotrigine oder andere Substanzen:**


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.


7. Cardiac Disorders
Consensus recommendations:

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”

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

### Cardiotoxicity as Long-term Side Effect

| Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.) | 2b | B |
| Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity | 1b | B |
| Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently: | 2b | B |
| ▪ Elderly patients, obesity, hypertension, hypercholesterinemia, i.e.-existing cardiac disease (incl. borderline LVEF), diabetes mellitus |  |
| Monitoring of cardiac function: |  |
| ▪ Standardized echocardiography (LVEF or SF in %) | 3b | C + |
| ▪ ECG (QT-interval) | 1a | A + |
| ▪ Troponin I as marker of cardiac toxicity | 2b | B +/- |
| Betablocker-prophylaxis during anthracycline therapy | 2a | B +/- |
“Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors.”

“Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)”


Troponin as Early Predictor for Cardiotoxicity


Betablocker-Prophylaxe


Adjuvant Trastuzumab
Cardiac Monitoring for CHF

Oxford LoE: 5 GR: D AGO: ++

Before start of trastuzumab
- History, physical examination (edema, hepatomegaly)
- Echocardiography (alternative to MUGA)

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

3 monthly assessment of LVEF

Statement: Cardiac Monitoring (5 D +++)
Vote result of the AGO recommendation: 100%


Feasibility of Treatment Combinations Considering Toxicities

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Regarding cardiac toxicity**
- Trastuzumab simultaneous to radiotherapy 2b B +
- Trastuzumab simultaneous to epirubicin 2b B +/-
- Trastuzumab simultaneous to doxorubicin 2b B -
- Anthracycline simultaneous to radiotherapy 2c C -

**Regarding lung and breast fibrosis**
- Tamoxifen simultaneous to radiotherapy 3 C +/-
- Chemotherapy simultaneous to radiotherapy 1b B -

---

**Trastuzumab simultaneous to radiotherapy**

**Trastuzumab simultaneous to epirubicin**
“Trastuzumab simultaneous to doxorubicin”

“Anthracycline simultaneous to radiotherapy”

“Tamoxifen simultaneous to radiotherapy”

8. Gastrointestinal Disorders

- Nausea, Emesis
- Mucositis
  - Stomatitis (Everolimus)
- Diarrhea
- Constipation
### Antiemetic Therapy

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

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>After assessment of emetic potential of chemotherapy protocol</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Neurokinin-1-receptor-antagonists</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Dexamethasone (also in chemotherapy combinations with ICPI)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>5-HT₃-antagonists</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Fixed antiemetic combination therapy</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Rescue Medication</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Levomepromazine, benzodiazepines</td>
<td>3b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Cannabinoids, ginger</td>
<td>3b</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

ICPi=Immune Checkpoint inhibitor


10. Keith B: Systematic review of the clinical effect of glucocorticoids on nonhematologic malignancy BMC Cancer (2008);8:84


Olanzapine


### ACUTE Nausea and Vomiting: SUMMARY

<table>
<thead>
<tr>
<th>EMETIC RISK GROUP</th>
<th>ANTIEMETICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Non-AC</td>
<td>5-HT(_3) + DEX + NK(_1) +/- OLZ*</td>
</tr>
<tr>
<td>High AC</td>
<td>5-HT(_3) + DEX + NK(_1) +/- OLZ*</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>5-HT(_3) + DEX + NK(_1)</td>
</tr>
<tr>
<td>Moderate (other than carboplatin)</td>
<td>5-HT(_3) + DEX</td>
</tr>
<tr>
<td>Low</td>
<td>5-HT(_3) or DEX or DOP</td>
</tr>
<tr>
<td>Minimal</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>

**5-HT\(_3\)** = serotonin receptor antagonist   **SE** = serotonin receptor agonist   **NK\(_1\)** = NK\(_1\)-receptor antagonist such as APOLOPIA or EQRAPENT or ROYALPINT or NEPH (combination of serotonin and norepinephrine)   **OLZ** = OLANZEPINE   **DOP** = dopamine receptor antagonist

**NOTE:** If the NK\(_1\) receptor antagonist is not available for AC chemotherapy, palonosetron is life preferred 5-HT\(_3\) receptor antagonist.

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

---

https://www.mascc.org/antiemetic-guidelines
### DELAYED Nausea and Vomiting: SUMMARY

<table>
<thead>
<tr>
<th>EMETIC RISK GROUP</th>
<th>ANTIEMETICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Non-AC</td>
<td>DEX or if APR 125mg for acute: MCP + DEX</td>
</tr>
<tr>
<td>High AC</td>
<td>NONE or if APR 125mg for acute: DEX or APR</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>NONE or if APR 125mg for acute: APR</td>
</tr>
<tr>
<td>Opioids, doxorubicin, or cyclophosphamide</td>
<td>DEX can be considered</td>
</tr>
<tr>
<td>Moderate (other)</td>
<td>No routine prophylaxis</td>
</tr>
<tr>
<td>Low and Minimal</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>

**Antiemetic Therapy**

[https://www.mascc.org/antiemetic-guidelines](https://www.mascc.org/antiemetic-guidelines)
Supportive Therapy

Antiemetics

<table>
<thead>
<tr>
<th>Wirkstoffgruppe</th>
<th>Substanz</th>
<th>Dosierung</th>
<th>Nebenwirkungen</th>
<th>Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin-antagonisten</td>
<td>Ondansetron</td>
<td>8 mg i.v., 4-8 mg p.o. 3 mg i.v., 5 mg p.o.</td>
<td>Kopfschmerzen, Transaminasenanstieg</td>
<td>sehr hoch</td>
</tr>
<tr>
<td>NK1-Antagonisten</td>
<td>Aprepitant</td>
<td>125 mg i.v., 25 mg p.o.</td>
<td>Kopfschmerzen, Transaminasenanstieg, Erbrechen</td>
<td>sehr hoch</td>
</tr>
<tr>
<td>Dopamin-antagonisten</td>
<td>Metoclopramid</td>
<td>bis zu 120 mg/d i.v. o.g.</td>
<td>Dyskinesien, Angstreaktion, Depression, Diarrhoe</td>
<td>hoch</td>
</tr>
<tr>
<td>Olanzepin</td>
<td>Olanzepin</td>
<td>10 mg/d for d1-4</td>
<td>Sedation, weight gain</td>
<td>hoch</td>
</tr>
<tr>
<td>Phenothiazine/Butyrophenone</td>
<td>Haloperidol</td>
<td>1-3 mg 4 x/d</td>
<td>Sedation, Senkung der Krampfschwelle, transiente Leberwerterhöhung</td>
<td>mäßig</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Dexamethason</td>
<td>8-30 mg i.v. 1-3 x/d</td>
<td>Blutzuckerentgleisung, psychiatrische Reaktion, Fluss, Blutdruckanstieg</td>
<td>mäßig</td>
</tr>
<tr>
<td>Metoclopramid</td>
<td>Metoclopramid</td>
<td>bis zu 120 mg/d i.v. o.g.</td>
<td>erhöhte Transaminase, Fluss, Blutdruckanstieg</td>
<td>mäßig</td>
</tr>
<tr>
<td>NEPA (Netupitant and Palonosetron)</td>
<td>NE 300 mg PA 0,5 mg</td>
<td></td>
<td>sehr hoch</td>
<td></td>
</tr>
</tbody>
</table>

Olanzapine
## Mucositis Prevention

https://www.mascc.org/mascc-guidelines

Multidisciplinary S3 guidelines of the AWMF (Reg.-Nr. 032-054OL): „Supportive Therapie bei onkologischen PatientInnen – interdisziplinäre Querschnittsleitlinie“

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2b</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

- Standardized mouth hygiene for prophylaxis of oral mucositis should be adhered to by all age groups and during all cancer-related therapies with any risk for oral mucositis.

This entails:

1. Patient:
   - Regular mouth washes (H2O, NaCl)
   - Soft toothbrushes
   - Interdental care: flossing or using interdental brush
   - Avoidance of alcohol, tobacco, hot food, sour food
   - Regular screening for lesions

2. Risk adjusted prophylaxis by dentist

3. Continuous clinical control

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

---

### Relevant practice guideline


Mucositis
https://www.mascc.org/mascc-guidelines

- Desinfecting / antiphlogistic measures:
  Mouth rinsing with infusions of chamomile or salvia, extracts of chamomile, etheric oils, polyvidon-iodine, hexetidine. Local therapy with crystal violet solution 0.5% or tinctura myrrhei, H. mometasonefuroate + propylene glycol

- Mucosa protecting measures (during / after application of chemotherapy):
  Sucking ice cubes (especially from pineapple juice) during 5-fluorouracile- or HD-melphalane. Calcium folinate (Leucovorin-mouth gel+) every 4-6 hrs for HD-methotrexate: do not start earlier than 24 hours after end of MTX-infusion (otherwise potential loss of efficacy of MTX!). Dexpantenole (Panthenol®-Solution. 5%) mouth rinsing.

- Local antimycotic treatment:
  Amphotericin B, nystatin, fluconazole

- Local antiviral treatment
  Aminoquinuride / tetracaine-HCl, Aciclovir®

- Local anaesthesia:
  Benzocaine, Doxepin 0,5% p.o.

- Pain Therapy: Opioids if indicated

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

- Adsorbent agents
  - Carbo medicinalis; cooline / pectine, Al-Mg-silicate hydrate

- Analgetics, opioids
  - Loperamide; codeine, morphine IV, tinctura opii (tincture of opium), butylscopolamine

- Off-label: Somatostatin-Analogon Octreotid s.c. (starting at grade 3)

- Pseudomembranous colitis
  - Metronidazole or (if not effective) vancomycin

- Initial dose escalation to reduce grade 3/4 diarrhea
  - CONTROL trial (dose escalation of neratinib: 120 mg/d day 1-7, 160 mg/d day 8-14, 240 mg/d afterwards)

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


treated with irinotecan." Support Care Cancer 2015;23;661-70.


**Constipation**

**Important Side Effect of Opioid Treatment**

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

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**Relevant practice guideline**

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,
9. Skin & Subcutaneous Tissue Disorders (Alopecia)

Relevant practice guideline
1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,
2. AWMF Registernummer: 032/054OL, http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html (Zugriff am 08.01.2020)
Skin Toxicities

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

* Substance- and regimen specific

Relevant practice guidelines
1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,

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

AGO: +/- LOE 2b B
  Primary Outcome: hair preservation
  Cooling: 50.5% success vs. 49.5% failure
  Non-cooling: 0% success vs. 100% failure
  Fisher’s exact test p < 0.001

Two Meta-analyses: AGO: +/- LOE 1b
- Scalp cooling reduced relative risk (RR) of alopecia by 43% (RR, 0.57; 95% CI, 0.45-0.72; I² = 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)

Side Effects According Organ Systems
Incidences, Prevention, Therapy

10. Musculoskeletal & connective tissue disorders
(see Chapter Osteoendocrinology)

Relevant practice guideline
1. Leitlinienprogramm Onkologie (Deutsche Krebgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,
11. General Disorders & Administration Site Conditions

Relevant practice guideline
1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.2, 2019,
2. AWMF Registernummer: 032/054OL, http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html (Zugriff am 08.01.2020)
Extravasation of Potentially Necrotizing Compounds (Anthracyclines, Taxanes, Vinorelbine)

- **Dexrazoxane for treatment of anthracycline-extravasations** (exception: liposomal Anthracyclines)
  - Oxford LoE: 2b
  - GR: B
  - AGO: ++

- **Hyaluronic acid for treatment of taxane/vinorelbine-extravasations (off-label use)**
  - Oxford LoE: 3b
  - GR: B
  - AGO: +

**Relevant practice guideline:**


2. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020, AWMF Registernummer: 032/054OL

**Dexrazoxane**


**Hyaluronsäure**

siehe S3-Leitlinie, Kapitel 11: Paravasate.
Extravasation of Chemotherapy
Role of Dexrazoxane / Hyaluronic Acid

Dexrazoxane for treatment of anthracyclines paravasates
Day 1: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs
Day 2: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs
Day 3: 500 mg/m² (max. 1000 mg), IV 1–2 hrs

Otherwise or if treatment with dexrazoxane is not indicated, following measures are recommended:
1. Local cooling: ice packs for 15 min every 6 hrs, for at least 3 days, alternatively: 24 h continuous ice cooling
2. Local application (with swab) of dimethylsulfoxid 99% (DMSO) every 3–4 hours for at least 3 days (better 14 days), allow it to air dry. The interval may be extended to 6 hours from day 4 onward.

Hyaluronic Acid in case of Taxan/Vinorelbin Paravasates:
- 1–10 Amp a 150 IU
- 1 ml dissolvent (e.g. NaCl 0.9%)
- Local anaesthesia
- No thermotherapy after taxanes
- Dry warmth 4 x daily 20 min during vincalaalkoids

Relevant practice guideline
1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, Februar 2020,
Side Effects According Organ Systems
Incidence, Prevention, Therapy

11. Lung

Relevant practice guideline
1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020,
2. AWMF Registernummer: 032/0540L, http://leitlinienprogramm-onkologie.de/Supportive-Therapie.95.0.html (Zugriff am 17.01.2022)
Drug-induced Pneumonitis, Interstitial Lung Disease (ILD)

- Diagnostic work-up with chest CT
- Therapy according to grade and drug*
  - Corticosteroids (start with $\geq 0.5\,\text{mg/kg/d}$ prednisolone-equivalent)  
  - Dose hold or therapy discontinuation* (according to respective product information)

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1. Leitlinienprogramm Onkologie (Deutsche Krebgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020, AWMF Registernummer: 032/0540L


Further Supportive and Palliative Issues

- **Orphan symptoms (from ESMO-guideline for orphan symptoms 2020):**
  - Muscle cramps
  - Myoclonus
  - Taste alterations
  - Dry mouth (Xerostomia)
  - Cough, Hiccup
  - Rectal tenesmus
  - Restless legs-syndrom

- **Further issues**
  - Nutrition
  - Pain management
  - Palliative Care

**Nutrition Deficiency**

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

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**Klinische Ernährung**


## Analgesia

- **Non-opioids; WHO Step 1**
  Diclofenac resinate, ibuprofen and / or metamizole, paracetamol (acetaminophen)

- **Mild opioids; WHO Step 2**
  Tramadol (preferentially „retard“-formulations) or tilidine / naloxone (also as „retard“-formulations)

- **Strong opioids; WHO Step 3**
  Morphine, buprenorphine (sublingual or transdermal), fentanyl (transdermal), hydromorphone, oxycodone, as a back-up levomethadone.
  The dose of opioids should be titrated step by step according to the analgetic effect.

- **Additional drugs – „adjuvants”**
  Canabinoide, Gabapentin, pregabalin, carbamazepine, amitriptyline, bisphosphonates

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**Relevant practice guideline:**


Palliative Care

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

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