Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Adjuvante zytostatische und zielgerichtete Therapien
Adjuvante zytostatische und zielgerichtete Therapien

- Versionen 2002 – 2018:
  Dall / Harbeck / Jackisch /Janni / Loibl / Lux /
  von Minckwitz / Möbus / Müller / Nitz /
  Schneeweiss / Simon / Schütz / Solomeyer /
  Stickeler / Thill / Thomssen / Untch

- Version 2019:
  Schmidt / Thomssen

Systematic review of published evidence
PUBMED 1999-2018
ASCO 1999-2018
SABCS 1999-2018
ECCO/ESMO 1999-2018
Subtyp-spezifische Strategien zur Systemtherapie

- Bei Indikation zur Chemotherapie neoadjuvante Applikation bevorzugt
  - Endokrine Therapie ohne Chemotherapie
  - HR+/HER2- mit „niedrigem Risiko” ++
    - Konventionell dosierte AT-basierte Chemotherapie (q3w)
    - Dosisdichte Chemotherapie (inkl. weekly-Regime) ++
    - Anschließend endokrine Therapie ++
- HR+/HER2- mit „hohem Risiko” +
  - Trastuzumab (plus Pertuzumab neoadjuvant bei hohem Risiko) ++
    - Sequentielles A/T-basiertes Regime mit simultaner Gabe von T + anti HER2-Th. ++
    - Anthrazyklin-freies, Platin-haltige Regime +
    - Anthrazyklin-freies, Taxan-haltige Regime +
- HER2+
  - Trastuzumab (plus Pertuzumab neoadjuvant bei hohem Risiko) ++
  - Konventionell dosierte AT-basierte Chemotherapie (q3w)
  - Dosisdichte sequentielle A/T-basierte Chemotherapie (inkl. weekly Schemata) ++
  - Neoadjuvante Platin-haltige Chemotherapie +

Systematic review of published evidence
PUBMED 1999-2018
ASCO 1999-2018
SABCS 1999-2018
ECCO/ESMO 1999-2018
<table>
<thead>
<tr>
<th>Schema</th>
<th>ED [mg/m²]</th>
<th>Gaben</th>
<th>kumulativ</th>
<th>mg/m²/Wo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Konventionelle Dosisdichte</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EC-Pac q3w</td>
<td>175</td>
<td>4</td>
<td>700</td>
<td>58,33</td>
</tr>
<tr>
<td><strong>Dosis-dichte Schemata</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ddEC-ddPac q2w</td>
<td>175</td>
<td>4</td>
<td>700</td>
<td>87,5</td>
</tr>
<tr>
<td>ddEC-Pw q1w</td>
<td>80</td>
<td>12</td>
<td>960</td>
<td>80</td>
</tr>
</tbody>
</table>
**Statement: Dosis-dicht Anthrazyklin-/ Taxan-basiert (inkl. weekly) LoE 1a A AGO ++**


4. Gray R et al. Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: An EBCTCG meta-analysis of 21,000 women in 16 randomised trials. SABCS 2017, abstr. GS1-01


Statement: Konventionell Anthrazyklin-/ Taxan-basiert (q3w) LoE 1a A AGO +


Statement: „Tailored“ Anthrazyklin-/ Taxan-basiert LoE 1b B AGO +/-


Statement: If anthracyclines cannot be given - Docetaxel plus cyclophosphamide

Statement: If anthracyclines cannot be given - Paclitaxel mono weekly


Statement: If anthracyclines cannot be given - CMF


Statement: Low dose maintenance Chemotherapy

Gray R et al. Increasing the dose-density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug administration significantly reduces both disease recurrence and breast cancer mortality: An EBCTCG meta-analysis of 21,000 women in 16 randomised trials. SABCS 2017, abstr. GS1-01
Statement: Dose-dense regimen

A60x4 - Pac175x4 - C600x4 q2w / ACPac / AC-Pac q2w

Statement: Dose-dense regimen

AC /EC q2w x 4 Pac q2w x 4

2. Burnell M et al. Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by


**Statement: Dose-dense regimen**

EC q2w / Pac q1w

EC q3w / Pac q1w


**EBCTCG Metaanalyse**

1. Gray R et al. Increasing the dose density of adjuvant chemotherapy by shortening intervals between courses or by sequential drug
administration significantly reduces both disease recurrence and breast cancer mortality: An EBCTCG meta-analysis of 21,000 women in 16 randomised trials. SABCS 2017, abstr. GS1-01

**Statement: Dose-dense and dose-escalated regimen (N ≥ 4+)**

**E-Pac-C q2w**


**Negative Trial**


### Empfohlene konventionelle Regime für die adjuvante Chemotherapie

<table>
<thead>
<tr>
<th>Anthracykl-/taxan-basierte Regime</th>
<th>Oxford</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>*EC q3w x 4 → Pwcq1w x 12</td>
<td>2b</td>
<td>++</td>
</tr>
<tr>
<td>*AC q3w x 4 → Pwcq1w x 12</td>
<td>1b</td>
<td>++</td>
</tr>
<tr>
<td>AC → D → qw3</td>
<td>1b</td>
<td>A+</td>
</tr>
<tr>
<td>*EC → D → qw3</td>
<td>1b</td>
<td>B+</td>
</tr>
<tr>
<td>DAC</td>
<td>1b</td>
<td>A+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anthracyklin-freie Regime</th>
<th>Oxford</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC entspricht EC → D</td>
<td>1b</td>
<td>B+</td>
</tr>
<tr>
<td>DC &gt;&gt; 4 x AC</td>
<td>1b</td>
<td>B+</td>
</tr>
<tr>
<td>Pac mono</td>
<td>1b</td>
<td>B+</td>
</tr>
<tr>
<td>CMF</td>
<td>1a</td>
<td>A+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Taxan-freie Schemata (bei pN0)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FE100C x 6</td>
<td>2b(1)</td>
<td>B+</td>
</tr>
<tr>
<td>F350E100C300 x 6</td>
<td>2b(1)</td>
<td>B+</td>
</tr>
</tbody>
</table>


Statement: Anthracycline/ taxane based regimen

*EC → Pw     E90C q3w x 4 → P80 qw1 x 12


Statement: Anthracycline/ taxane based regimen

AC → Pw A60Cq3w x 4 → P80qw1 x 12


Statement: Anthracycline/ taxane based regimen
AC → D A60C q3w x 4 → D100 qw3 x 4
EC → D E90C q3w x 4 → D100 qw3 x 4


Statement: Anthracycline/taxane based regimen
DAC → D75A50C q3w x 6


Statement: Anthracycline-free regimen
DC → D75 C600 x4 corresponds to EC → D

1. Harbeck N et al. No age-related outcome disparities according to 21-gene recurrence score groups in early breast cancer patients treated by adjuvant chemotherapy in the prospective WSG PlanB trial. SABCS 2017, abstr.P1-06-06

Statement: Anthracykline-free regimen
DC >> 4 x AC


Statement: Anthracycline-free regimen
Pac mono 80 mg q1w x 4-6


Statement: Anthracycline-free regimen

CMF 600/40/600 mg q3w x 6


Statement: Taxan-freie Schemata (bei pN0)

FE100C x 6 q3w


2. Thomssen C, Vetter M, Kantelhardt EJ et al. on behalf of the NNBC-3 Study Group Adjuvant therapy with FEC and docetaxel in high risk node-negative breast cancer patients identified by tumor-biological (uPA/PAI-1) or clinico-pathological risk assessment. A joint trial of AGO-Breast Study Group, German Breast Group and EORTC Pathology and Biomarker Group (NNBC 3-Europe).Submitted
Statement: Capecitabine containing regimen in TNBC


Statement: Capecitabine containing regimen in TNBC in general:

Statement: Capecitabine containing regimen in TNBC as postneoadjuvant therapy if non-pCR:


Statement: 5- Fluorouracile added to EC/AC=>Pac


Statement: Platinum containing regimen in TNBC

6. Sikov WM et al. Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast


### Statement Trastuzumab + Pertuzumab (N+ and/or HR- / N- and HR+)


### Statements: Trastuzumab in node-negative disease (if chemotherapy is indicated)


7. Jackisch C et al. Efficacy and safety of subcutaneous or intravenous trastuzumab in patients with HER2-positive early breast cancer after 5 years' treatment-free follow-up: Final analysis from the phase III, open-label, randomized HannaH study. SABCS 2017, abstr. PD3-11


Statements: >10 mm/> 5-10 mm/ <= 5mm


Statement: Start of treatment simultaneously with taxanes


Statement s.c.

Statement: Duration

*Duration Trastuzumab 1 year*

*Duration Trastuzumab 2 year*

*Duration Trastuzumab 0.5 years*

1. Goldhirsch A et al.; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive


4. Joensuu H et al. A randomized phase III study of adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer (the SOLD study). SABCS 2017, abstr. GS3-04


Metaanalysis:

### Statement: with paclitaxel/docetaxel after AC/EC


### Statement: P q1w12 without A in pT < 2 cm pN0


2. Tolaney SM et al. Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). Journal of Clinical Oncology 2017;35:15 suppl: 511-511

### Statement: with docetaxel and carboplatin


Statement: Trastuzumab + Pertuzumab simultaneously with Paclitaxel q1w or Docetaxel q3w (after EC or AC)


Statement: Trastuzumab + Pertuzumab simultaneously with Docetaxel and Carboplatin q3w


Statement: Trastuzumab + Pertuzumab simultaneously with taxanes dose-dense


Statement: radiotherapy concurrent with trastuzumab
1. M. Y. Halyard, T. M. Pisansky, L. J. Solin et al. Trastuzumab can be administered concurrent to adjuvant radiotherapy of the breast or thoracic wall. Adjuvant radiotherapy (RT) and trastuzumab in stage I-IIA breast cancer: Toxicity data from North Central Cancer Treatment Group Phase III trial N9831 J Clin Oncol. 2009;27(16):2638-44
Adjuvante Therapie mit weiteren zielgerichteten Substanzen

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b*</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>1b*</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>1b</td>
<td>B</td>
<td>--</td>
</tr>
</tbody>
</table>

Statement: with Lapatinib

Delayed adjuvant treatment


3. Perez EA et al. Disease-free survival (DFS) in the lapatinib alone arm and expanded results of the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) in the adjuvant treatment of HER2-positive early breast cancer (EBC) ESMO 2014

Statement: with Lapatinib + Trastuzumab

Statement: Bevacizumab


Statement ER and/or PgR positiv (pCR und non-pCR) Endokrine Therapie nach Menopausenstatus (s. Kap. 10)


etc.

Statement HER2 positiv (bei pCR): Low risk: Trastuzumab (bis 12 Mon. komplett)

Statement HER2 positiv (bei pCR): pN+ oder HR-: Trastuzumab + Pertuzumab (bis 12 Mon. komplett)

Statement HER2 positiv (bei non-pCR) T-DM1 (bis 12 Mon. anti-HER2-Therapie komplett)

Statement HER2 positiv (bei non-pCR) Neratinib nach 1 Jahr Trastuzumab (nur bei HR-positiv)

Statement Tripelnegativ (TNBC) (bei non-pCR) Capecitabine (8 Kurse)
Biosimilars
Generelle Überlegungen

Biosimilars, die in der Therapie (z.B. Trastuzumab) und Supportivtherapie des Mammakarzinoms (z.B. GCSF) eingesetzt werden, müssen vor dem Einsatz in der täglichen Routine den von den Zulassungsbehörden (EMA, FDA) geforderten Entwicklungs- und Zulassungsprozess erfolgreich durchlaufen haben.*
