Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Neoadjuvante
(Primäre) systemische Therapie
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
- HR+/HER2- mit „niedrigem Risiko”
  - Endokrine Therapie ohne Chemotherapie
  - Endokrine Therapie mit Chemotherapie
- HR+/HER2- mit „hohem Risiko”
  - Konventionell dosierte AT-basierte Chemotherapie (q3w)
  - Dosisdichte Chemotherapie (inkl. weekly Regime)
  - Anschließend endokrine Therapie
- HER2+
  - 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
- Triple-negativ (TNBC)
  - 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
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Dosisdichte Schemata sind folgende Schemata

1) q3w gegebene Dosis als q2w gegeben mit primärem G-CSF Support.
   Z.B. Paclitaxel 175mg/m² q2w == Paclitaxel 87,5 mg/m²/week (Pq2w)

2) Wöchentliche Schemata, die im Vergleich zum parallelen q3w-Schema eine relativate Dosisverdichtung aufweist.
   Z.B. Paclitaxel weekly 80-90 mg/m² (week(Pw))

### Dosisdichte Paclitaxel

<table>
<thead>
<tr>
<th>Schema</th>
<th>ED [mg/m²]</th>
<th>Gaben</th>
<th>kumulativ</th>
<th>mg/m²/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC-Pac q3w</td>
<td>175</td>
<td>4</td>
<td>700</td>
<td>58,33</td>
</tr>
<tr>
<td>ddEC-ddPac</td>
<td>175</td>
<td>4</td>
<td>700</td>
<td>87,5</td>
</tr>
<tr>
<td>ddEC-Pw</td>
<td>80</td>
<td>12</td>
<td>960</td>
<td>80</td>
</tr>
</tbody>
</table>
Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number)


Pathological complete response is associated with improved survival in all subgroups


4. Yee D, et al. Pathological complete response predicts event-free and distant disease free survival in the I-SPY 2 Trial. SABCS 2017 (abs GS3-08)

Can achieve operability in primary inoperable tumors


Improved options for breast conserving surgery


Reduces the rate of lymphadenectomies


Allows individualization of therapy according to mid-course treatment effect

Allows individualization of post-neoadjuvant treatment


Inflammatory breast cancer


Inoperable breast cancer


Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation


If similar postoperative adjuvant chemotherapy is indicated


Young age

cT1 / cT2 tumors o. N0 o. G3

**Negative ER and PgR status**


**Triple negative breast cancer (TNBC)**


**Positive HER2 status**

the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145

Non-lobular tumor type

Early clinical response
Multigene signature


Ki-67

Tumour infiltrating lymphocytes

PIK3CA mutation
1. Loibl S, et al. PIK3CA mutations are associated with lower rates of pathologic complete response to anti-human epidermal growth factor receptor 2 (her2) therapy in primary HER2-overexpressing breast cancer. J Clin Oncol 2014: 32; 3212

**gBRCA mutation**


**HRD**

Standard regimens used in the adjuvant setting with a duration of at least 18 weeks


AC or EC → D q3w or P q1w


Taxane followed by anthracycline sequence


Platinum in TNBC (irrespective of BRCA status)


**Nab-Paclitaxel weekly instead of Paclitaxel weekly**


Breast ultrasound
Palpation


Mammography


MRI


PET(-CT)


Clip tumour region


Trastuzumab in combination with chemotherapy


Pertuzumab + Trastuzumab in combination with chemotherapy


4. Gianni L et al. Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). J Clin Oncol 33, 2015 (suppl; abstr 505)


Lapatinib in combination with chemotherapy


Lapatinib + Trastuzumab in combination with chemotherapy


Two anti-HER2 agents without chemotherapy


Anti-HER2 agent in combination with endocrine treatment

1. Rimawi MF, et al. SABCS 2014 (S6-02)


Complete all chemotherapy before surgery i.e. ≥ 18 weeks of treatment


In case of response after 2 cycles of DAC in HR positive breast cancer consider 8 instead of 6 cycles of DAC

In case of no change:
Completion of NST, followed by surgery


Continuation of NST with non-cross-resistant regimen
AC or EC x 4 → D x 4 or Pw x 12

1. Bear HD, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and


DAC x 2 → NX x 4


In case of progressive disease:
Stop of NST and immediate surgery or radiotherapy


Additional adjuvant chemotherapy with non-cross-resistant regimen


Mark previous tumor region


**Surgery**


<table>
<thead>
<tr>
<th>Item</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative Clipmarkierung der Tumorregion</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Adäquate Operation nach NACT</td>
<td>2b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Mikroskopisch freie Absetzungsränder</td>
<td>2</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Exzision innerhalb neuer Grenzen nach aktueller Bildgebung</td>
<td>2</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

**Microscopically clear margins**

**Tumor resection according to imaging result**

**Sentinel node biopsy (see chapter “Surgery”)**


Complete Axillary lymph node dissection after positive sentinel lymph node may be omitted in certain cases due to lack of benefit in prospectively randomized studies.


Statement surgical intervention in the axilla before or after neoadjuvant chemotherapy


Positive margins after repeated excisions


Radiotherapy not feasible


In case of clinical complete response:

Inflammatory breast cancer in case of pCR


Multicentric lesions

cT4a-c breast cancer
Initiation of therapy after histologic diagnosis


Surgery after the nadir of the leucocyte count (2 to 4 weeks after last course of chemotherapy)


Radiotherapy after surgery 2–3 weeks after surgery BCS

Postmenopausal patients:
Who are inoperable and can / will not receive chemotherapy


Optimizes the option for breast conserving therapy


Aromatase inhibitors (for > 3 months)


AI and fulvestrant

Concurrent chemo-endocrine therapy


Prognostic scores following NST


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)