Neoadjuvant chemotherapy (NACT) in young women with breast cancer

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Department of Oncology, Aarhus University Hospital
"Young women" according to EUSOMA guidelines

- Is under the age of 40
- Special issues related to:
  - Fertility preservation
  - Pregnancy and lactation
  - Contraception
  - Body image and sexuality
  - BRCA 1 and BRCA 2
Epidemiology

- Breast cancer accounts for 30-40% of all cancers in women below 40
- About 7% of all new breast cancers are in women below 40
- Only slightly increasing incidence over time
- More frequently associated with a family history
Why consider neoadjuvant chemotherapy in young women with early breast cancer?

• According to DBCG guidelines women < 40 are recommended chemotherapy despite histopathology, so NACT because:
  – A need to preserve the breast
  – more often triple neg breast cancer
  – no co-morbidity
  – BRCA status not ready
Neoadjuvant vs. adjuvant chemotherapy: OS, DFS and RFS

**A**
- Survival (%)
- HR = 0.99, P = .90
- Trt: Post-Op AC 751 Deaths 315
- Pre-Op AC 742

**B**
- Disease-Free (%)
- HR = 0.93, P = .27
- Trt: Post-Op AC 751 Events 434
- Pre-Op AC 742

**C**
- Relapse-Free (%)
- HR = 0.98, P = .78
- Trt: Post-Op AC 751 Events 293
- Pre-Op AC 742

**NSABP B-18**
- Operable Breast Cancer
- **Stratification**
  - Age
  - Clinical Tumor Size
  - Clinical Nodal Status
- Operation
  - AC x 4

*Rastogi and Wolmark 2008 JCO*
Neoadjuvant vs. adjuvant chemotherapy: DFS and age < 50 years

Trend in favor of preoperative chemotherapy in DFS and OS for women less than 50y

OS: HR=0.81, P=0.06

Rastogi and Wolmark 2008 JCO
pCR and disease-free/overall survival

DFS HR = 0.47, P < 0.0001
pCR and disease-free/overall survival

**NSABP B-27**

Operable Breast Cancer → Randomization

- AC x 4 Tam X 5 Yrs → Surgery
- AC x 4 Tam X 5 Yrs → Docetaxel x 4 → Surgery
- AC x 4 Tam X 5 Yrs → Docetaxel x 4

**DFS HR = 0.49, P < 0.0001**

B-27: Effect of adding T to pre-operative AC

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Rastogi and Wolmark 2008 JCO
Neoadjuvant vs. adjuvant chemotherapy: a meta-analysis

The ability to do less surgery after NAC does not seem to be associated with any risk for the patient

Mittendorf E et al, Ann Surg 2013
Update 2015: 2% LRR at 8 years !!!

Modified from Poortmans et al. Sem Rad Oncol 2012; Bartelink et al R&O 2012
Management of the axilla in case of NACT

Pathological Complete Response Rates in the Axilla

- **Triple Negative**: 49.4%
- **HER2 Positive**: 64.7%
- **HR Positive, HER2 Negative**: 21.1%

*p<0.0001*

Boughey et al, Ann Surg, in press
Timing of sentinel node procedure

<table>
<thead>
<tr>
<th>Pre NACT</th>
<th>Post NACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal staging before start treatment</td>
<td>Detection rate (80 - 90%)</td>
</tr>
<tr>
<td>Detection rate (99%)</td>
<td>FNR (10-15%)</td>
</tr>
<tr>
<td>FNR (8%)</td>
<td>FNR &lt; 7% if combined with removal of clipped node (TAD)</td>
</tr>
</tbody>
</table>

C. van Deurzen, EJC 2009
J. Boughey, JAMA 2013
T. Kuehn, Lancet Oncology 2013
J. Boughey, Annals Surg 2016
S. Abigail, JCO 2016
Which neoadjuvant chemotherapy regimen to chose for young women?

- Consensus that the regimen should include anthracyclines and taxanes
- TNBC should not impact on choice of therapy
- Subsets of patients with BRCA mutations might need different treatment approach

Long term side effects of (neo) adjuvant chemotherapy – knowledge is important for the young women

- Chronic fatigue
- Ovarian failure
  - Infertility
  - Hot flushes
  - Bone loss
  - Sexual problems
- Cardiovascular disease
- Cognitive function
- Secondary malignancies

Costs/Side effects | Benefits
"Young women" according to EUSOMA guidelines

- Is under the age of 40
- Special issues related to:
  - Fertility preservation → Cryopreservation, Zoladex
  - Pregnancy and lactation → Centralized treatment
  - Contraception → Barriere, IUD, no hormones
  - Body image and sexuality → Mastectomy versus BCS
  - BRCA 1 and BRCA 2 → Accelerated genetic testing

Moore H, NEJM 2015
"The German experience"

DOI 10.1007/s10549-015-3479-z

Outcome after neoadjuvant chemotherapy in young breast cancer patients: a pooled analysis of individual patient data from eight prospectively randomized controlled trials

Sibylle Loibl¹² · Christian Jackisch² · Bianca Lederer¹ · Michael Untch³ · Stefan Paepke⁴ · Sherko Kümmer⁵ · Andreas Schneeweiss⁶ · Jens Huober⁷ · Jörn Hilfrich⁸ · Claus Hanusch⁹ · Bernd Gerber¹⁰ · Holger Eidtmann¹¹ · Carsten Denkert¹² · Serban Dan Costa¹³ · Jens-Uwe Blöhmer¹⁴ · Valentina Nekljudova¹ · Keyur Mehta¹ · Gunter von Minckwitz¹

CLINICAL TRIAL

CrossMark
Pooled analysis of individual patient data from eight prospective randomized trials from 1998 to 2010

- Gepar Duo
- Gepar Trio
- Gepar Quattro
- AGO 1
- Prepare
- Techno
- Gepar Quinto
- The Gapardo trial

All trials used and anthracycline and taxane based chemotherapy backbone

Objectives and endpoints

• To evaluate the pCR rate in women < 40 years compared to age groups 40-49 years and >= 50 years

• To access the effect of age on disease free survival (DFS), local recurrence free survival (LRFS), distant free survival (DFS) and overall survival (OS) according to pCR status in different subgroups

Baseline characteristics of women undergoing treatment in 8 prospective trials of NACT

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>&lt; 40 years N=1453</th>
<th>&gt;= 40-49 years N=3073</th>
<th>&gt; 50 years N=4423</th>
<th>All patients N=8949</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>cT1</td>
<td>135 9.4 %</td>
<td>251 8.2 %</td>
<td>248 5.7 %</td>
<td>634 7.1 %</td>
<td></td>
</tr>
<tr>
<td>cT2</td>
<td>984 68.3 %</td>
<td>1978 64.9 %</td>
<td>2704 61.7 %</td>
<td>5666 63.1 %</td>
<td></td>
</tr>
<tr>
<td>cT3</td>
<td>215 14.9 %</td>
<td>537 17.6 %</td>
<td>713 16.3 %</td>
<td>1465 16.5 %</td>
<td></td>
</tr>
<tr>
<td>cT4a-c</td>
<td>56 3.9 %</td>
<td>162 5.3 %</td>
<td>388 8.8 %</td>
<td>606 8.8 %</td>
<td></td>
</tr>
<tr>
<td>cT4d</td>
<td>50 3.5 %</td>
<td>120 3.9 %</td>
<td>333 7.6 %</td>
<td>503 7.6 %</td>
<td></td>
</tr>
<tr>
<td><strong>Nodal status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>cN0</td>
<td>731 51.6 %</td>
<td>1499 49.7 %</td>
<td>2069 47.6 %</td>
<td>4299 49.0 %</td>
<td></td>
</tr>
<tr>
<td>cN1</td>
<td>619 43.7 %</td>
<td>1372 45.5 %</td>
<td>1996 45.9 %</td>
<td>3987 45.4 %</td>
<td></td>
</tr>
<tr>
<td>cN2</td>
<td>50 3.5 %</td>
<td>110 3.6 %</td>
<td>216 5.0 %</td>
<td>376 4.3 %</td>
<td></td>
</tr>
<tr>
<td>cN3</td>
<td>18 1.3 %</td>
<td>33 1.1 %</td>
<td>68 1.6 %</td>
<td>119 1.4 %</td>
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<tr>
<td>Histological type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Ductal invasive</td>
<td>1221 (85.7%)</td>
<td>2448 (81.6%)</td>
<td>3432 (78.9%)</td>
<td>7101 (81.0%)</td>
<td></td>
</tr>
<tr>
<td>Lobular invasive</td>
<td>86 (6.0%)</td>
<td>354 (11.8%)</td>
<td>626 (14.4%)</td>
<td>1066 (12.2%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>117 (8.2%)</td>
<td>197 (6.6%)</td>
<td>290 (6.7%)</td>
<td>604 (6.9%)</td>
<td></td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>1</td>
<td>42 (3.1%)</td>
<td>124 (4.2%)</td>
<td>149 (3.6%)</td>
<td>315 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>684 (49.8%)</td>
<td>1639 (55.9%)</td>
<td>2334 (55.8%)</td>
<td>4657 (54.9%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>647 (47.1%)</td>
<td>1170 (39.9%)</td>
<td>1698 (40.6%)</td>
<td>3515 (41.4%)</td>
<td></td>
</tr>
</tbody>
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Baseline characteristics of women undergoing treatment in 8 prospective trials of NACT

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<tr>
<td>Subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ER pos/HER-2 neg (G1-2)</td>
<td>330 31.2 %</td>
<td>877 38.2 %</td>
<td>1271 40.2 %</td>
<td>2478 38.0 %</td>
<td></td>
</tr>
<tr>
<td>ER pos/HER-2 neg (G3)</td>
<td>133 12.6 %</td>
<td>293 12.8 %</td>
<td>440 13.9 %</td>
<td>866 13.3 %</td>
<td></td>
</tr>
<tr>
<td>ER pos/HER2 pos</td>
<td>174 15.9 %</td>
<td>379 15.9 %</td>
<td>455 13.8 %</td>
<td>1008 13.8 %</td>
<td></td>
</tr>
<tr>
<td>ER neg/HER2 pos</td>
<td>137 12.5 %</td>
<td>243 10.2 %</td>
<td>393 11.9 %</td>
<td>773 11.9 %</td>
<td></td>
</tr>
<tr>
<td>Triple neg</td>
<td>323 29.4 %</td>
<td>589 24.7 %</td>
<td>733 22.3 %</td>
<td>1645 22.3 %</td>
<td></td>
</tr>
</tbody>
</table>

Correlation between age and pCR

Fig. 1 Correlation between age and pCR. STEPP-like analysis of age and pathological complete response (pCR, ypT0 ypN0)

The odds of achieving a pCR by subtype and age

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>pCR (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>overall</td>
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</tr>
<tr>
<td>&lt;40</td>
<td>20.9</td>
<td>1.42 (1.21, 1.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40-49</td>
<td>17.7</td>
<td>1.29 (1.12, 1.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;=50</td>
<td>13.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>11.0</td>
<td>1.78 (1.23, 2.68)</td>
<td>0.002</td>
</tr>
<tr>
<td>40-49</td>
<td>8.4</td>
<td>1.43 (1.06, 1.92)</td>
<td>0.018</td>
</tr>
<tr>
<td>&gt;=50</td>
<td>5.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR+/HER2+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>19.0</td>
<td>0.98 (0.60, 1.60)</td>
<td>0.938</td>
</tr>
<tr>
<td>40-49</td>
<td>18.7</td>
<td>0.98 (0.68, 1.43)</td>
<td>0.932</td>
</tr>
<tr>
<td>&gt;=50</td>
<td>18.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-/HER2-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>29.2</td>
<td>0.89 (0.57, 1.40)</td>
<td>0.622</td>
</tr>
<tr>
<td>40-49</td>
<td>30.0</td>
<td>0.82 (0.57, 1.18)</td>
<td>0.290</td>
</tr>
<tr>
<td>&gt;=50</td>
<td>33.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNBC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>39.3</td>
<td>1.64 (1.22, 2.19)</td>
<td>0.031</td>
</tr>
<tr>
<td>40-49</td>
<td>37.0</td>
<td>1.50 (1.24, 2.03)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

pCR, pathological complete response; CI, confidence interval; HR, hormone receptor; TNBC, triple negative breast cancer

Survival in age groups with or without pCR

Survival in age groups with or without pCR

Worse survival in ER pos/HER-2 neg young women with no pCR

Soft trial
Exemestane + OFS beneficial among young women < 35 years with high risk disease

*28% relative reduction in risk of subsequent invasive cancer or death
*34% relative reduction in recurrence of breast cancer
*>96% of women alive at 5 years
*No significant difference in survival; conclusions about survival premature after 5yr follow-up of HR+ breast cancer

Francis, PA NEJM (2015)
Future strategies will reduce chemotherapy prescription

“In the entire MINDACT population, the trial confirmed the hypothesis that the «genomic» strategy leads to a 14% reduction in CT prescription versus the «clinical» strategy”

“Among the High risk patients, the clinical use of MammaPrint® is associated with a 46% reduction in chemotherapy prescription”
Future perspectives in young women

• To optimize adjuvant endocrine therapy in young women with ER pos/HER-2 neg BC having no pCR after NACT

• To do SN (sentinel node biopsy) after NACT in a safe manner and spare patients from ALND if downstaged from a positive to a negative LN status

• New prognostic tools in order not to overtreat young women!

• The optimal chemotherapy regimen regarding efficacy and long-term tolerance
Thank you