Adjuvant chemotherapy in older breast cancer patients: how to decide?

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Wildiers H, Kunkler I, … Lancet Oncol 2007
**Tumor extent:**
- T (tumor size)
- N (nodal status)

**Tumor biology**
- Luminal A
- Luminal B HER2 neg
- Triple negative
- Her2+

**General health status:**
Geriatric assessment

**Patient preference**

Chemo indication depends on …
When tumor size $\uparrow$ and N status $\uparrow$

- Relative benefit of chemo $\approx$
- Risk of relapse $\uparrow$
- Absolute benefit of chemo $\uparrow$

Adjuvant online for elderly?  (Br J Cancer 2012 Monfardini et al)

- 272 women $\geq$70y
- 47% fit, 32% vulnerable, 21% frail
- In ER pos, higher choice for CT with adj online use (35-39% CT) versus CGA use (10% CT)
General health status

Cause of death in elderly

- A sizeable proportion of elderly with operable breast cancer dies of NON-CANCER-related causes.

- Cause of death: 14000 pt 5y FUP

<table>
<thead>
<tr>
<th>Total deaths</th>
<th>Deaths from breast cancer</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–69</td>
<td>1334</td>
<td>933</td>
</tr>
<tr>
<td>70–74</td>
<td>514</td>
<td>293</td>
</tr>
<tr>
<td>75–79</td>
<td>696</td>
<td>329</td>
</tr>
<tr>
<td>≥80</td>
<td>1681</td>
<td>663</td>
</tr>
<tr>
<td>Total</td>
<td>4225</td>
<td>2218</td>
</tr>
</tbody>
</table>

British Journal of Cancer (2011) 104, 564 – 570
Performance of two geriatric screening tools in older cancer patients

G8
(Soubeyran et al. 2008)

- Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
- Weight loss during the last 3 months
- Mobility
- Neuropsychological problems
- Body Mass Index (weight in kg/height in m2)
- Takes more than 3 medications per day
- In comparison with other people of the same age, how does the patient consider his/her health status?
- Age
### Tumor biology

<table>
<thead>
<tr>
<th>Intrinsic subtype</th>
<th>Clinico-pathologic surrogate definition</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td><strong>‘Luminal A-like’</strong>&lt;br&gt;all of:&lt;br&gt;ER and PgR positive&lt;br&gt;HER2 negative&lt;br&gt;Ki-67 ‘low’&lt;br&gt;Recurrence risk ‘low’ based on multi-gene-expression assay (if available)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>The cut-off point between ‘high’ and ‘low’ values for Ki-67 varies between laboratories. A level of &lt;14% best correlated with the gene-expression definition of Luminal A based on the results in a single reference laboratory [23]. Similarly, the added value of PgR in distinguishing between ‘Luminal A-like’ and ‘Luminal B-like’ subtypes derives from the work of Prat et al. which used a PgR cut-off point of ≥20% to best correspond to Luminal A subtype [24]. Quality assurance programmes are essential for laboratories reporting these results.</td>
</tr>
<tr>
<td>Luminal B</td>
<td><strong>‘Luminal B-like (HER2 negative)’</strong>&lt;br&gt;ER positive&lt;br&gt;HER2 negative and at least one of:&lt;br&gt;Ki-67 ‘high’&lt;br&gt;PgR ‘negative or low’&lt;br&gt;Recurrence risk ‘high’ based on multi-gene-expression assay (if available)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>‘Luminal B-like’ disease comprises those luminal cases which lack the characteristics noted above for ‘Luminal A-like’ disease. Thus, either a high Ki-67&lt;sup&gt;4&lt;/sup&gt; value or a low PgR value (see above) may be used to distinguish between ‘Luminal A-like’ and ‘Luminal B-like (HER2 negative)’.</td>
</tr>
<tr>
<td>Erb-B2 overexpression</td>
<td><strong>‘HER2 positive (non-luminal)’</strong>&lt;br&gt;HER2 over-expressed or amplified&lt;br&gt;ER and PgR absent</td>
<td></td>
</tr>
<tr>
<td>‘Basal-like’</td>
<td><strong>‘Triple negative (ductal)’</strong>&lt;br&gt;ER and PgR absent&lt;br&gt;HER2 negative</td>
<td>There is an 80% overlap between ‘triple-negative’ and intrinsic ‘basal-like’ subtype. Some cases with low-positive ER staining may cluster with non-luminal subtypes on gene-expression analysis. ‘Triple negative’ also includes some special histological types such as adenoid cystic carcinoma.</td>
</tr>
</tbody>
</table>
## Tumor biology

### Subtype distribution

<table>
<thead>
<tr>
<th></th>
<th>Basal like</th>
<th>Her2+</th>
<th>Luminal A</th>
<th>Luminal B HER2 neg</th>
<th>Luminal B HER2+</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary surgery</strong></td>
<td>162</td>
<td>65</td>
<td>586</td>
<td>765</td>
<td>93</td>
<td>1671</td>
<td>83.5%</td>
</tr>
<tr>
<td><strong>Neoadjuvant</strong></td>
<td>21</td>
<td>21</td>
<td>52</td>
<td>85</td>
<td>20</td>
<td>199</td>
<td>9.9%</td>
</tr>
<tr>
<td><strong>Metastatic</strong></td>
<td>11</td>
<td>14</td>
<td>38</td>
<td>60</td>
<td>12</td>
<td>135</td>
<td>6.6%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>194</td>
<td>100</td>
<td>676</td>
<td>910</td>
<td>125</td>
<td>2005</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Percentage</strong></td>
<td>9.7%</td>
<td>5.0%</td>
<td>33.7%</td>
<td>45.4%</td>
<td>6.2%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

2005 new diagnosis breast cancer pts ≥65y from 2000 till 2010 in UZLeuven

Own data UZLeuven 2013
- About 35% of tumors in 70+
- Adj. Hormonal therapy = cornerstone of adjuvant systemic therapy
- Adj. Chemotherapy in general population: very limited benefit
- Adj. Chemotherapy in elderly: no indication, even in higher volume tumors.
Luminal B HER2 neg

- About 45% of tumors in 70+
- Adj. Hormonal therapy
  - = cornerstone of adjuvant systemic therapy
- Adj. Chemotherapy in general population:
  - Benefit in general, but limited in size
  - genetic profiling might help for chemo decision.
- Adj. Chemotherapy in elderly:
  - probably more limited benefit.
  - Genetic profiling might help for chemo decision.
700 pts (+ 1100-1300 not included i.e. low GG or other causes followed up)

1/ 4-yr OS 2/ Tolerance, DFS, QoL (ELD15), Q-TWiST, G8, cost-effectiveness analysis, GG/RT-PCR, TR, geriatrics

Arm A = HT**
Arm B = CT + HT**

NO CHEMOTHERAPY IS RECOMMENDED
Follow up + inclusions in other studies (e.g ELD15 validation)
- Low GG
- Other causes for non inclusion (refusal, geriatrics, etc.)
Patients will be offered HT according to standard guidelines

Phase III w/ 4-yr OS
Hypothesis B > A
\( \Delta \) 7.5% (A 80% vs B 87.5%) HR 0.60
Inclusion period 4 years
170/year
Follow up 4 years
129 events
\( \alpha \) 5% \( \beta \) 20%
340 pts/arm

Courtesy to E. Brain
About 10% of tumors in 70+

Worst prognosis but heterogeneous tumor type!

Adj. Chemotherapy in general population: most beneficial

Adj. Chemotherapy in elderly: for high risk subtypes potentially beneficial
Study: 475 triple neg breast cancers: age trends

Dreyer ... Wildiers.
The breast 2013
Tumor biology

Selection of 395 pts who received primary surgery

Selection of 294 pts with IDC-NOS who received primary surgery

Multivariable Cox model for DFS for patients with IDC-NOS, receiving primary surgery ($n = 294$).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect</th>
<th>Estimate</th>
<th>Hazard ratio (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>+10 yrs</td>
<td>-0.47</td>
<td>0.63 (0.48 0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymph node invasion</td>
<td>Yes vs no</td>
<td>0.89</td>
<td>2.43 (1.38 4.27)</td>
<td>0.002</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>Yes vs no</td>
<td>-1.53</td>
<td>0.22 (0.09 0.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjuvant radiotherapy</td>
<td>Yes vs no</td>
<td>-1.24</td>
<td>0.29 (0.16 0.54)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Aapre and Wildiers.
Ann Oncol 2012
Dreyer … Wildiers.
The Breast 2013
Invasive breast cancer
Age ≥65y
ER pos 66%
ER neg 34%

Stratification: 65-69, 70-79, > 79

6 CMF or 4 AC (n=226)
6 capecitabine (n=307)

H.B. Muss et al. (NEJM 360 2055)

- capecitabine: 2 toxic deaths (2500 mg/m²)
- Significant benefit in OS and DFS (mainly in HR negative)

Tumor biology

CALGB 49907

Triple neg.

DFS

CMF/AC
Cape
p=0.00009

Overall survival

CMF/AC
Cape
p=0.019
About 10% of tumors in 70+ (ER+ and ER-)

Prognosis dramatically improved with chemotherapy + anti-HER2 therapy

Adj. Chemotherapy + antiHER2 in general population:

- dramatic improvement of prognosis, even in pT1bN0

Adj. Chemotherapy + antiHER2 in elderly:

- Certainly to consider
- Anti-HER2 without chemo for those not tolerating chemo?
Tumor biology

- No age effect for benefit of trastuzumab (and chemotherapy!)

**HER2+**

Supplemental Figure 2. Forest plot for event hazard ratios corresponding to disease-free survival (DFS): squares = hazard ratios and 95% confidence intervals; hazard ratios less than one favor trastuzumab.

NSABP B-31 NEJM
2005 Romond
But increased cardiotoxicity with trastuzumab in elderly! HR 1.95 (1.75-2.17); CHF 29.4% with T; 18.9% without T

Congestive hearth failure free survival

Fig 1. Congestive heart failure (CHF)-free survival for patients with breast cancer, time since breast cancer diagnosis to first CHF claim (in months). (A) According to trastuzumab use. (B) According to trastuzumab and anthracycline use. AT, anthracycline and trastuzumab; A_noT, anthracycline and no trastuzumab; T_noA, trastuzumab and no anthracycline; noAT, no anthracycline or trastuzumab.

JCO 2013 Chavez-MacGregor
Mandelblatt et al (JCO 2010)
- 934 pts ≥65y
- High risk group (ER neg and/or N+): 69% received CT
- Others (ER pos and N-): 16% received CT
- Patient choice for CT depended on
  - preference for smaller absolute benefit
  - high risk setting
  - higher rating of provider communication

Ring et al (Ann Oncol 2013)
- 803 pts ≥70y
- 116 (14%) offered CT (independent factors associated were young age, high risk of recurrence, and better performance status)
- 66 (8%) received CT
Which chemo/regimen?

- **CMF** in elderly:
  - less tolerated and less effective than in younger (JCO 18 1412; BMC cancer 5 30)
  - 1.28% toxic death if ≥ 65 y (lancet 354 130)

- **Anthracyclines** in elderly:
  - Anthracyclines superior to CMF: no age trend
  - 10-year cardiac failure rate in women 66-70 y (JCO 25 3308) **38%**

- **Taxanes**
  - 4 TC > 4 AC (JCO 27 1177)
  - Paclitaxel weekly: slightly inferior to AC but less toxic; 12w = 18w.
    (ASCO 2013 abstr 1007); with trastuzumab acceptable regimen (SABCS 2014 S1-04))
  - Sequential anthracycline and taxane (AC->taxol, FEC->docetaxel)
  - Higher risk of dose delay, reduction, hospitalisation, toxicity: growth factor use generally required
Conclusion

Tumor extent:
T (tumor size)
N (nodal status)

Tumor biology
Luminal A
Luminal B HER2 neg
Triple negative Her2+

Chemo indication depends on …

General health status:
Geriatric assessment

Patient preference