Pathologic complete response is not a valid surrogate for long-term outcome for early-stage breast cancer

Debates and Didactics in Hematology and Oncology, August 8th, Sea Island, GA

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Association of PCR and outcome by breast cancer subtype

Cortazar et al Lancet 2014
Prognostic impact of pathologic complete response (pCR) on disease-free survival according to breast cancer intrinsic subtype.

**PCR rate and outcome according to subtype**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percent PCR</th>
<th>Importance of PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>&lt; 10%</td>
<td>Not important</td>
</tr>
<tr>
<td>Luminal B (HER2-negative)</td>
<td>20%</td>
<td>Probably</td>
</tr>
<tr>
<td>HER2-positive, ER-positive</td>
<td>10 to 30%</td>
<td>Maybe</td>
</tr>
<tr>
<td>HER2-positive, ER-negative</td>
<td>50 to 60%</td>
<td>Probably but not conclusive</td>
</tr>
<tr>
<td>Triple negative</td>
<td>30%</td>
<td>Probably</td>
</tr>
</tbody>
</table>
Phase 2 trial of pre-operative therapy tailored by 21-gene recurrence score

Goserelin added to exemestane if premenopausal
TC = docetaxel plus cyclophosphamide
* Given to maximal response

Zelnak et al Proc ASCO 2013
Pathologic complete response (PCR) is consistently lower in ER+ HER2+ breast cancers compared to ER- HER2+ breast cancers. 

Reviewed in Nahta and O'Regan BRCT 2012

pCR Correlates With Better EFS in Subsets of BC, Including HER2+ BC: a FDA led Meta-Analysis
(N = 11,955 / 1,989 HER2+)

PCR is prognostic in ER- cancer but not ER+ cancers that co-express HER2

Likelihood of PCR is inversely related to level of ER expression for HER2+ breast cancers
Intrinsic subtyping of HER2-positive breast cancers

HR-positive

HER2 17%
LUM A 17%
LUM B 48%
Basal 34%
Claudin-low 1%
Normal 1%

N = 156

HR-negative

HER2 5%
LUM A 5%
LUM B 3%
Basal 24%
Claudin-low 3%
Normal 51%

N = 109

Carey et al. Proc ASCO 2014

Phase III NeoALTTO Study Design

Baseline

6 weeks
Lapatinib
Trastuzumab
Lapatinib + trastuzumab

12 weeks
Lapatinib + paclitaxel
Trastuzumab + paclitaxel
Lapatinib + trastuzumab + paclitaxel

Surgery

9 weeks
FEC x 3

34 weeks
Lapatinib
Trastuzumab
Lapatinib + trastuzumab

Blood sample
PET/CT scan

Radiotherapy (if indicated)

NeoALTTO Primary Outcome Measure: pCR*

<table>
<thead>
<tr>
<th></th>
<th>Lapatinib n = 154</th>
<th>Trastuzumab n = 149</th>
<th>Lapatinib + Trastuzumab n = 152</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR HR+ Subset</td>
<td>16%</td>
<td>23%</td>
<td>42%</td>
<td>0.03</td>
</tr>
<tr>
<td>pCR HR- Subset</td>
<td>34%</td>
<td>37%</td>
<td>61%</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*pPathologic complete response (pCR) rate defined as the absence of invasive cancer in the breast at the time of surgery.

NeoALTTO: Does pCR Translate Into Improved EFS and OS?

- Found correlation between pCR and EFS and OS
- 3-year EFS was 86% for those who achieved pCR, 72% for those who did not (P = 0.0003)
- OS was 94% for those who achieved pCR, 87% for those who did not (P = 0.005)
- Most notable in HR-negative disease
- Not powered to detect difference in survival between study arms

DISEASE-FREE SURVIVAL (DFS) ANALYSIS

DFS BY Hormone Receptor Status

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting

Interaction tests $p = 0.70 \ L + T$

$ p = 0.60 \ T \rightarrow \ L$

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting
Importance of pathologic complete response

Overall Survival

Recurrence is directly related to amount of cancer in the breast

Increasing amount of cancer
PCR is not predictive for the majority of breast cancers

- PCR is very low for luminal A cancers and is not predictive of outcome
- PCR is low for luminal B cancers and maybe predictive of outcome (chemotherapy not the answer for these cancers)
- PCR is predictive for ER-negative cancers but a subset of patients have a favorable outcome without achieving PCR
- PCR probably not important for most HER2-positive, ER-positive cancers