Neoadjuvant Chemotherapy in Breast Cancer: Patient Selection and Predictors of pCR

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Neoadjuvant Chemotherapy

• Indications:
  • Management of locally advanced invasive breast cancers including inflammatory breast cancer
  • ‘Down-staging’ of large inoperable cancers to permit surgical resection
  • Routine management of women with high risk disease who would require adjuvant chemotherapy based on biological tumour characteristics and clinical-radiological findings
Neoadjuvant Therapy

- Ability to monitor treatment response and tailor subsequent locoregional and systemic therapy -> more individualised patient care
  - Patients with pCR may not benefit from further regional therapy such as adjuvant radiotherapy
  - Patients with poor response can be identified and entered into trials of novel targeted agents

- Evaluation of treatment response to new agents using pathological complete response (pCR) as a surrogate marker of outcome
  - Neoadjuvant studies smaller, cheaper, faster results
  - Patient selection critical – well-characterised high risk pop’n
Pre Treatment Evaluation - Breast

- Pre treatment breast core biopsy must be adequate for unequivocal diagnosis of invasive carcinoma and assessment of key prognostic/predictive factors
  - Histological type and grade
  - ER/ (PR) status
  - HER2 status
  - Other biomarkers
    - Ki67, multigene assays
    - additional markers needed for trial e.g. AR, TILs

- If multiple lesions biopsy of at least 2 foci is advised to confirm multifocality and look for heterogeneity
Pre Treatment Evaluation - Breast

- If there is an inadequate amount of invasive carcinoma in the core repeat biopsy should be considered.
- Particular care should be taken if:
  - Biopsy predominantly DCIS, especially in context of Ca++ with no mass
  - Papillary carcinoma with focal invasion – radiological size may overestimate invasive component
### Predictors of pCR

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Pathological complete response (%)</th>
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<tbody>
<tr>
<td><strong>Clinical tumour stage</strong></td>
<td></td>
</tr>
<tr>
<td>T1 (n=785)</td>
<td>18.3 (15.7-21.2)</td>
</tr>
<tr>
<td>T2 (n=7328)</td>
<td>19.9 (19.0-20.9)</td>
</tr>
<tr>
<td>T3 (n=2493)</td>
<td>13.0 (11.7-14.3)</td>
</tr>
<tr>
<td>T4a-c (n=781)</td>
<td>14.5 (12.1-17.1)</td>
</tr>
<tr>
<td>T4d (n=482)</td>
<td>16.0 (12.8-19.6)</td>
</tr>
<tr>
<td><strong>Clinical nodal status</strong></td>
<td></td>
</tr>
<tr>
<td>Negative (n=6320)</td>
<td>18.8 (17.9-19.8)</td>
</tr>
<tr>
<td>Positive (n=5487)</td>
<td>16.9 (15.9-17.9)</td>
</tr>
<tr>
<td><strong>Histological type</strong></td>
<td></td>
</tr>
<tr>
<td>Ductal (n=8567)</td>
<td>15.5 (14.7-16.3)</td>
</tr>
<tr>
<td>Lobular (n=1221)</td>
<td>7.8 (6.3-9.4)</td>
</tr>
<tr>
<td>Mixed (n=475)</td>
<td>27.7 (19.0-26.8)</td>
</tr>
<tr>
<td><strong>Tumour grade</strong></td>
<td></td>
</tr>
<tr>
<td>1 (n=425)</td>
<td>7.8 (5.4-10.7)</td>
</tr>
<tr>
<td>2 (n=4392)</td>
<td>12.3 (11.3-13.3)</td>
</tr>
<tr>
<td>3 (n=3217)</td>
<td>25.8 (24.3-27.4)</td>
</tr>
<tr>
<td><strong>Clinical tumour subtype</strong></td>
<td></td>
</tr>
<tr>
<td>Hormone-receptor-positive, HER2-negative, grade 1/2 (n=1986)</td>
<td>7.5 (6.3-8.7)</td>
</tr>
<tr>
<td>Hormone-receptor-positive, HER2-negative, grade 3 (n=630)</td>
<td>16.2 (13.4-19.3)</td>
</tr>
<tr>
<td>HER2-positive, hormone-receptor-positive, trastuzumab (n=385)</td>
<td>30.9 (26.3-35.8)</td>
</tr>
<tr>
<td>HER2-positive, hormone-receptor-positive, no trastuzumab (n=701)</td>
<td>18.3 (15.5-21.3)</td>
</tr>
<tr>
<td>HER2-negative, hormone-receptor-negative, trastuzumab (n=364)</td>
<td>50.3 (45.0-55.5)</td>
</tr>
<tr>
<td>HER2-negative, hormone-receptor-negative, no trastuzumab (n=471)</td>
<td>30.2 (26.0-34.5)</td>
</tr>
<tr>
<td>Triple negative (n=1157)</td>
<td>33.6 (30.9-36.4)</td>
</tr>
</tbody>
</table>

Cortazar et al., Lancet 2014;384(9938):164-72
Predictors of pCR

Cortazar et al., Lancet 2014;384(9938):164-72
pCR by tumour subtype

- HR +ve tumours have low pCR rates BUT better survival
- HER2+ and triple negative cancers more likely to achieve pCR, but overall prognosis is worse with poor DFS and OS if no pCR

<table>
<thead>
<tr>
<th>Tumour Subtype</th>
<th>pCR</th>
<th>3y DFS</th>
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<tbody>
<tr>
<td>HR+/HER2-</td>
<td>2-8%</td>
<td>91-96%</td>
</tr>
<tr>
<td>HR+/HER2+</td>
<td>8-33%</td>
<td>82-90%</td>
</tr>
<tr>
<td>HR-/HER2+</td>
<td>33-52%</td>
<td>33-68%</td>
</tr>
<tr>
<td>HR-/HER2-</td>
<td>24-38%</td>
<td>65-67%</td>
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</table>
pCR by tumour subtype - axilla

- ACOSOG Z1071
- Nodal pCR rate 41%
- ER+/HER2- = 21%, TN = 49%, HER2+ = 65%

Residual Cancer Burden

Symmans W F et al. JCO 2017;35:1049-60.

TNBC

Luminal HER2-ve
Residual Cancer Burden

HER2+ Chemo only

HER2+ chemo plus anti-HER2 Rx

Symmans W F et al. JCO 2017;35:1049-60.
Predictors of response in ER+/HER2 negative cancers
- Grade
- PR status
- High Ki67
- Ductal NST tumours respond better than special types – lobular, tubular, mucinous
Predictors of response in ER+/HER2 negative cancers

- **Grade**
  - Grade 1-2: pCR rate 7.5% (6-9%)
  - Grade 3: pCR rate 16% (13-19%)
Predictors of response in ER+/HER2 negative cancers

- Invasive lobular carcinoma
- Lower rate of pCR compared with matched ER+ NST
  \[\text{ILC} = 3-6\% \text{ v NST 14-17\%}\]
- Cortazar analysis:
  \[\text{ILC} = 7.8\% (6.3-9.4\%) \text{ v NST 15.5\% (14.7-16.3\%)}\]
- BUT also lower rate of downstaging and BCS
  \[\text{ILC} = 35.4\% \text{ v NST 54.8\%}\]
- Mastectomy rate remained higher in ILC on multivariate analysis
- Lobular phenotype a significant predictor of no response within luminal B cancers in one series

Petrelli et al., BCRT 2013:142;227-35. Balmoltivola et al., Breast Ca Res Tr 2014;148:511-23
Response by tumour subtype - Luminal

- Cambridge data
- Audit of tumour downstaging and response post NACT
- 6 lobular cancers – none showed a reduction in size post NACT
- 2 cases size underestimated by MRI

Courtesy of A. Agrawal.
Response by tumour subtype - Luminal

- MSKCC – review of ER+ /HER2- cancers who received NACT looking for predictors of downstaging
- Overall pCR rate 5% - breast 7%, cN+ - axilla 15%
- Downstaging to BCS - ILC 16% versus ductal NST 48%
- Axillary downstaging – ILC 7% versus NST 16% (N/S)
- Grade 3 – BCS 51% (v 33%) and axillary pCR 26% (v 5%)
- PR neg – BCS 52% (v 36%) and axillary pCR 22% (v 11%)
- Multivariate model – greatest benefit in PR-/G3 -> BCS 62% and axillary pCR 35%

Biomarkers – ki67

- Neoadjuvant studies; high Ki67 associated with increase in pCR rate in several series but no data on benefit of specific Rx arms
- Difficult to interpret as often include all molecular subtypes
- Persisting questions regarding methodology and optimum cut offs
- One study suggests a cut off of >40% but includes HER2+ and TNBC. Luminal B higher rate than luminal A defined by cut off > 14% (pCR 3% vs 13%) Wang et al., Medicine 2016;95(18).

- Another proposed cut off of >50% but there were too few pCR in the ER+/HER2- group for meaningful analysis Alba et al., The Oncologist 2016;21:150-55.
Biomarkers – ki67

- Denkert et al., Ann Onc 2013
- Pre treatment Ki67 levels in GeparTrio trial

- Low Ki67 (<15%) – pCR = 4%
- Intermediate Ki67 (15-35%) – pCR = 13%
- High Ki67 (>35%) – pCR = 29%

- Ki67 predictive of pCR for luminal HER2- and TN but not HER2+ subtypes
- Ki67 only associated with survival in luminal HER2- group
Biomarkers – ki67

- Fasching et al., BMC Cancer 2011;11:486.
- Series looking specifically at ER+/HER2- tumours suggest cut off of 13-20%

- Chen et al., BCRT 2018 Epub
- Cut off of 25.5% to distinguish responders from non-responders amongst ER+ tumours

- Jones et al., BCRT 2009
- Pre treatment – High Ki67 predictive of pCR
- Post treatment – High Ki67 associated with worse RFS and OS

- Sheri et al., BCRT 2017;164:395-400
- Both pre treatment Ki67 and IHC4 score associated with pCR
Genomic tests

- PAM50 has also been shown to predict survival outcomes in chemotherapy treated populations and pCR rates post neoadjuvant chemotherapy
  
  - ISPY-1 and NOAH neoadjuvant trials both PAM50 subtype and high ROR score were associated with increased rates of pCR
    
  
  - Oncotype Dx - an analysis of the chemotherapy arm of the NSABP B-20 trial showed chemotherapy benefit for patients with a high RS but minimal or no benefit with a low RS; no specific data in neoadjuvant chemotherapy setting
    
    Paik et al., J Clin Onc 2006;24:3726-34.
  
  - EndoPredict - associated with pCR following neoadjuvant chemotherapy in a single study (EP low 7% pCR; EP high 17% pCR)
    
    Bertucci et al., Cancer Letts 2014;355:70-5.
pCR by tumour subtype – HER2+

Predictors of response in HER2 positive cancers

- **ER status**
  - ER+: pCR rate with trastuzumab 31% (26-36%)
  - ER-: pCR rate with trastuzumab 50% (45-56%)

Cortazar et al., Lancet 2014;384(9938):164-72
pCR by tumour subtype – HER2

- Retrospective analysis of NOAH study looking at PAM50 subtypes
- Only 55% of HER2+ tumours HER2-E subtype; 21% luminal, 7% basal-like, 18% normal-like
- Better pCR rates in HER2-E vs luminal HER2+ tumours (53% v 29%) with larger improvement in EFS with addition of Trastuzumab

pCR by tumour subtype – HER2+

Predictors of response in HER2 positive cancers

- In the NEOSPHERE trial, higher levels of HER2 protein expression associated with pCR after dual targeted Rx

FISH:
- higher HER2:CEP17 ratio – OR = 2.11, optimum cut off 4.5
- higher HER2 copy number – OR = 1.15, optimum cut off 14
  Wu et al., Oncotargets and Therapy 2018;11:801-8
- Higher pCR rate with high level amplification (copy number >10) than low level amplification (6-10) – 55% v 24%
- No difference in RFS or OS
  Guiu et al., BrJC 2010;103:1335-42.
pCR by tumour subtype - TNBC

- 7 subtypes of triple negative breast cancer
- Different rates of pCR between subtypes
- No difference in OS – LAR group had low pCR rate but best survival at 3 years

pCR by tumour subtype - TNBC

- Lower pCR rates amongst some special types of TNBC
- Metaplastic carcinoma – low rates of pCR in several series with higher rates of progressive disease
- Majority of studies not using current regimes with platinum based therapy

- Medullary-like carcinoma???
- High levels of TILS
- High proliferation
- BRCA1 dysfunction and impaired DNA repair
  => all associated with improved response to NACT
Immune response - TILS

- Increased levels of TILs pre Rx associated with pCR
- Highest lymphocyte density in HER2+ tumours

High levels of TILs associated with pCR in a meta-analysis of 8 studies (OR 3.93)

Subset analysis showed this was true for ER- (OR 3.30), HER2+ (OR 5.05) and TNBC (OR 2.49) but not ER+ disease

Retained significance in multivariate analysis

High pre treatment TILs associated with improved survival outcomes in HER2+ patients in neo-ALLTO trial
Salgado et al., JAMA Oncol 2015; 1:448-54.

Immune related gene expression signatures also associated with pCR

Absence of inflammation a predictor of no response