Managing Triple Negative Breast Cancer: Chemotherapy in Everyday Practice

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Triple Negative Breast Cancer by Subtype

Defined by clinical assays:
- ER- PR- HER2-

Molecular assays:
- 3/4 molecularly "appropriate"
- 1/4 are not what they seem

Prat and Perou, Molec Oncol 2010
What Are ER or PR “Borderline” Tumors?

- Borderline ER or PR (1-10%), HER2-negative:
  - 46% Luminal
  - 17% Basal-like
  - 29% HER2-enriched

No assumptions. 
Use endocrine therapy.

Cheang M et al, ASCO 2012
TNBC and Treatment: What Do We Know?

• Prognosis can be accurately estimated by the usual variables.

• Chemotherapy is the only known therapy.

Everything else is theory.
Prognosis in TNBC

**T3N1 TNBC**

- ~80% 10-year risk of relapse
- (-24% = benefit of 3rd generation chemotherapy)
- 55% 10-year risk of death

From www.adjuvantonline.com
AdjuvantOnline and TNBC

T1aN0 TNBC

Shared Decision Making

Name: ___________________________ (Breast Cancer)
Age: 50 General Health: Excellent

Estrogen Receptor Status: Negative  Histologic Grade: 2
Tumor Size: 0.1 - 1.0 cm  Nodes Involved: 0
Chemotherapy Regimen: Third Generation Regimen

Decision: No Additional Therapy

19% relapse at 10 years
8% death

“Relapse” includes in-breast and local recurrence, new primaries and true relapse.

In TNBC, 10-year mortality may be better metric for decision-making

79 out of 100 women are alive and without cancer in 10 years.
19 out of 100 women relapse.
2 out of 100 women die of other causes.
Absolute benefit of chemotherapy depends on absolute risk.

TNBC is an independent risk factor for relapse, however numbers relapsing in this setting are small.
There Are Good Prognosis TNBC

T1a-bN0, untreated
Distant RFS at 5 y

Ok to not treat small, node negative TNBC.

Gonzalez-Angulo et al, JCO 2009
### Is Conventional Chemotherapy Effective?

- **360 patients**
- **Anthracycline/taxane-treated**
- **Overall pathologic complete response (pCR) rate = 22%**
- **Modified PAM50 molecular subtyping**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Residual disease</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-like</td>
<td>47 (58%)</td>
<td>34 (42%)</td>
</tr>
<tr>
<td>Claudin-low</td>
<td>29 (67%)</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>31 (63%)</td>
<td>18 (37%)</td>
</tr>
<tr>
<td>LumA</td>
<td>110 (98%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>LumB</td>
<td>56 (85%)</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Normal-like</td>
<td>13 (76%)</td>
<td>4 (24%)</td>
</tr>
</tbody>
</table>

Adapted from Cheang, SABCS 2011

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**Take Home:**

1. **Basal-like and Claudin-Low (majority of TNBC) are sensitive to conventional agents.**
2. **In (neo)adjuvant studies, underlying population is key to interpreting results.**
## Are There Better Choices?

**Table 1: Summary of completed neoadjuvant chemotherapy trials.**

<table>
<thead>
<tr>
<th>Clinical trials</th>
<th>Design</th>
<th>Drugs</th>
<th>Population</th>
<th>pCR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver et al. [12]</td>
<td>Phase II single arm</td>
<td>Cisplatin × 4</td>
<td>TNBC</td>
<td><strong>6/28 (21%)</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td>Byrski et al. [13]</td>
<td>Retrosp.</td>
<td>All; CMF; AD; AC/FAC; cisplatin</td>
<td></td>
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<tr>
<td></td>
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<td><strong>BRCA1 mut.</strong></td>
</tr>
</tbody>
</table>
| Bear et al. [14]         | Phase III random. | Arm 1A: D × 4 → AC × 4  
Arm 1B: D + X × 4 → AC × 4  
Arm 1C: D + G × 4 cycles → Ac × 4 | HER2–         | Arm 1A: 102/393 (26%)  
Arm 1B: 91/390 (23%)  
Arm 1C: 106/388 (27%) |
| Alba et al. [15]         | Phase II random. | Arm A: EC × 4 cycles → D × 4  
Arm B: EC × 4 cycles → D + Carbo × 4 | Basal-like    | Arm A: 14/46 (30%)  
Arm B: 14/47 (30%) |
| Zelnak et al. [16]       | Phase II random. | Arm A: D × 4 cycles → X × 4;  
Arm B: D + X × 8 cycles. | HER2–         | Arm A: 2/25 (8%)  
Arm B: 3/26 (12%)  
Arm A/B (TNBC): 4/21 (19%) |
| Von Minckwitz et al. [17] | Phase III random. | Arm 1 (responder): TAC × 4  
Arm 2 (responder): TAC × 6  
Arm 3 (nonresponder): TAC × 4  
Arm 4 (nonresponder): VX × 4 | Any breast cancer | Arm 1–4  
TNBC: 77/198 (39%)  
Non-TNBC: 22/147 (15%) |
| Huober et al. [18]       | Phase II single arm | Ixabepilone × 4                         | Any breast cancer | TNBC: 11/42 (26%)  
Non-TNBC: 18/119 (15%) |
| Baselga et al. [19]      |             |                                            |               |                |
Local Recurrence and TNBC

2009
40 yo woman T1N1 TNBC, treated with BCT, adjuvant AC-T, RT

2013
Mass adjacent to lumpectomy site – biopsy + TNBC
Mastectomy – T2Nx

What about adjuvant systemic therapy?
Chemotherapy Prolongs Survival for Isolated Local or Regional Recurrence of Breast Cancer: The CALOR Trial


Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer. IBCSG 27–02, NSABP B–37, BIG 1–02 (BOOG, GEICAM, IBCSG)
• First, isolated, ipsilateral, resectable recurrence
  – IBTR or CW recurrence
  – Axillary or IM LN
• Fully excised

CALOR

Strata
  • Prior Chemo-Tx
  • ER+ and/or PR+
  • Location ILRR

RANDOMIZE

Chemotherapy
> 1 drug, 3-6 cycles

No chemotherapy

+ Endocrine therapy for ER+ and/or PR+
+ HER2-directed therapy (optional)
– INADEQUATE POWER
  • Sample size (optimal 977) = 162

– PROTOCOL DEVIATIONS
  • Polychemotherapy recommended – 31% monotherapy

– CHEMOTHERAPY BENEFIT UNCERTAIN
  • ~65% hormone receptor-positive
  • > 50% IBTR
  • Average disease-free interval = 5 years
CALOR: Disease-Free Survival

Aebi S et al, SABCS 2012
## Neoadjuvant Bevacizumab

### Table 2: Summary of neoadjuvant bevacizumab-based chemotherapy trials.*

<table>
<thead>
<tr>
<th>Clinical trials</th>
<th>Design</th>
<th>Drugs</th>
<th>Population</th>
<th>Status</th>
<th>pCR rate</th>
</tr>
</thead>
</table>
| Gerber et al. [31]   | Phase III    | Arm 1: EC × 4 → D × 4  
                       | Arm 2: EC + Bev × 4 → D + Bev × 4          | TNBC       | Completed | Arm 1: 96/342 (28%)  
                       |              | Arm 2: 119/327 (36.4%)                      |            |                      |
| Bear et al. [14]     | Phase III    | Arm 1A-C: Anthracycline-taxane-based      | HER2−      | Completed | TNBC Bev: 121/236 (51%)  
                       | random      | chemotherapy   
                       | Arm 2A-C: Anthracycline-taxane-based      |            |                      | TNBC/no Bev: 115/243 (47%) |
|                      |              | chemotherapy + Bev                          |            |                      | HR+ Bev: 82/352 (23%)  
                       |              |                                            |            |                      | HR+/no Bev: 53/349 (15%)  |
| CALGB-40603          | Phase II     | Arm 1: T → AC  
                       | Arm 2: T + Bev → AC + Bev                 | TNBC       | Ongoing   | —                         |
|                      | random       | Arm 3: T + Carbo → AC                        |            |                      |                           |
|                      |              | Arm 4: T + Carbo + B → AC + Bev             |            |                      |                           |

*TNBC: triple-negative breast cancer; pCR: pathological complete response; Bev: bevacizumab; T: paclitaxel; Carbo: carboplatin; D: docetaxel; C: cyclophosphamide; A: doxorubicin; E: epirubicin.

SABCS 2013!!?

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- **Bevacizumab in TNBC?**
  - **Modest signal in metastatic and neoadjuvant setting**
  - **No effect as single agent in adjuvant setting**
  - **Need a way to select for response!**

Amos K et al, Int J Breast Cancer 2012
Primary results of BEATRICE, a randomized phase III trial evaluating adjuvant bevacizumab-containing therapy in triple-negative breast cancer

D Cameron\(^1\), J Brown\(^2\), R Dent\(^3\), C Jackisch\(^4\), J Mackey\(^5\), X Pivot\(^6\), G Steger\(^7\), T Suter\(^8\), M Toi\(^9\), M Parmar\(^10\), L Bubuteishvili-Pacaud\(^11\), V Henschel\(^11\), R Laefle\(^11\), R Bell\(^12\)

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**Resected triple-negative\(^a\) (centrally confirmed) invasive early breast cancer (N=2591)**

- Investigator’s choice of standard CT (4–8 cycles) → Observation
- Investigator’s choice of standard CT (4–8 cycles)
  - BEV (5 mg/kg/wk equivalent) → BEV monotherapy (total duration 1 year)
BEATRICE: Invasive Disease-Free Survival

Cameron D et al, SABCS 2012
Summary

• “TNBC” is made up of a variety of subtypes. This may be the future of therapy.
• Clinical variables are important in prognostication in TNBC.
• Conventional chemotherapy is standard (neo)adjuvant treatment. Alternatives, e.g. platinum regimens, show promise in BRCA+.
• Isolated locoregional recurrence should be managed with local therapy + “re” adjuvant Rx.
  - Options in pretreated: TC, CMF
Thanks!