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.
**T1a/bN0 TNBC and Outcome**

- 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,
ode negative TNBC.

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

<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>

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

Adapted from Cheang, SABCS 2011

**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.
<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>6/28 (21%)</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Byrski et al. [13]</td>
<td>Retros.</td>
<td>All; CMF; AD; AC/FAC; cisplatin</td>
<td></td>
<td>BRCA1 mut.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cisplatin: 10/12 (83%)</td>
</tr>
<tr>
<td>Bear et al. [14]</td>
<td>Phase III random.</td>
<td>Arm 1A: D × 4 → AC × 4</td>
<td>HER2−</td>
<td>Arm 1A: 102/393 (26%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 1B: D + X × 4 → AC × 4</td>
<td></td>
<td>Arm 1B: 91/390 (23%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 1C: D + G × 4 cycles → Ac × 4</td>
<td></td>
<td>Arm 1C: 106/388 (27%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm B: EC × 4 cycles → D + Carbo × 4</td>
<td></td>
<td>Arm B: 14/47 (30%)</td>
</tr>
<tr>
<td>Zelnak et al. [16]</td>
<td>Phase II random.</td>
<td>Arm A: D × 4 cycles → X × 4; Arm B: D + X × 8 cycles.</td>
<td>HER2−</td>
<td>Arm A: 2/25 (8%)</td>
</tr>
<tr>
<td>Huober et al. [18]</td>
<td></td>
<td>Arm 2 (responder): TAC × 6</td>
<td></td>
<td>TNBC: 77/198 (39%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 3 (nonresponder): TAC × 4</td>
<td></td>
<td>Non-TNBC: 22/147 (15%)</td>
</tr>
<tr>
<td>Baselga et al. [19]</td>
<td>Phase II single arm</td>
<td>Ixabepilone × 4</td>
<td>Any breast cancer</td>
<td>TNBC: 11/42 (26%)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Non-TNBC: 18/119 (15%)</td>
</tr>
</tbody>
</table>

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

Amos K et al, Int J Breast Cancer 2012
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

**Surgery**
- 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)
CALOR: Challenges

– 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
## 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>
<tbody>
<tr>
<td>Gerber et al. [31]</td>
<td>Phase III</td>
<td>Arm 1: EC × 4 → D × 4</td>
<td>TNBC</td>
<td>Completed</td>
<td>Arm 1: 96/342 (28%)</td>
</tr>
<tr>
<td>(GeparQuinto)</td>
<td></td>
<td>Arm 2: EC + Bev × 4 → D + Bev × 4</td>
<td></td>
<td></td>
<td>Arm 2: 119/327 (36.4%)</td>
</tr>
<tr>
<td>Bear et al. [14]</td>
<td>Phase III</td>
<td>Arm 1A-C: Anthracycline-taxane-based</td>
<td>HER2−</td>
<td>Completed</td>
<td>All Arms Bev: 203/588 (35%)</td>
</tr>
<tr>
<td>(NSABP B-40)</td>
<td>random</td>
<td>chemotherapy</td>
<td></td>
<td></td>
<td>All Arms/no Bev: 168/592 (28%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 2A-C: Anthracycline-taxane-based</td>
<td></td>
<td></td>
<td>TNBC Bev: 121/236 (51%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>chemotherapy + Bev</td>
<td></td>
<td></td>
<td>TNBC/no Bev: 115/243 (47%)</td>
</tr>
<tr>
<td>CALGB-40603</td>
<td>Phase II</td>
<td>Arm 1: T → AC</td>
<td>TNBC</td>
<td>Ongoing</td>
<td>HR+ Bev: 82/352 (23%)</td>
</tr>
<tr>
<td></td>
<td>random</td>
<td>Arm 2: T + Bev → AC + Bev</td>
<td></td>
<td></td>
<td>HR+/no Bev: 53/349 (15%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 3: T + Carbo → AC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 4: T + Carbo + B → AC + Bev</td>
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<td></td>
</tr>
</tbody>
</table>

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

Amos K et al, Int J Breast Cancer 2012

SABCS 2013!!?
Primary results of BEATRICE, a randomized phase III trial evaluating adjuvant bevacizumab-containing therapy in triple-negative breast cancer

D Cameron¹, J Brown², R Dent³, C Jackisch⁴, J Mackey⁵, X Pivot⁶, G Steger⁷, T Suter⁸, M Toi⁹, M Parmar¹⁰, L Bubuteishvili-Pacaud¹¹, V Henschel¹¹, R Laeufle¹¹, R Bell¹²

- Resected triple-negative (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)
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!
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!