Overview

- Inflammatory breast cancer vs. LABC
  - Prognosis is different
  - Subtypes exist
- Importance of a pCR
  - TNBC vs. other
- Utilizing optimal chemotherapy
  - Platinum agents
- The need to “target” TNBC
  - Angiogenesis
  - JAK-STAT pathway

Inflammatory Breast Cancer vs. LABC:
Different Biology – yet Subtypes Exist
IBC vs. LABC: Different Prognosis

- Seer 2004-7: 2-yr BCS
  - IBC = 84%
  - LABC = 91%
  - P < .0001
- 43% higher risk of breast cancer death in IBC vs. LABC

OS:
- HR = 1.98 for IBC v LABC
- Median OS: 2.9 yr v 6.4 yr
- 5 yr OS: ER+ = 50%
- ER- = 25%

43% higher risk of breast cancer death in IBC vs. LABC

IBC: Rate of Local/Regional Recurrence According to Breast Cancer Subtype.

IBC: Overall Survival According to Breast Cancer Subtype.
Neoadjuvant Treatment of TNBC: Importance of a pathologic complete response

“TNBC Paradox”

Cytotoxic Therapy for TNBC: Effective Current Treatment
Advances in Chemotherapy Have Dramatically Improved Outcomes in ER-Negative Breast Cancer

Corresponds to an absolute improvement in 5-year DFS of 23%, and to an absolute improvement in 5-year OS of 17% in ER-negative subset

Berry et al, JAMA 2006

DFS With or Without Paclitaxel in CALGB 9344 According to ER/HER2 Status


Prognostic Impact of pCR on DFS According to Breast Cancer Intrinsic Subtype

von Minckwitz G et al. JCO 2012;30:1796-1804
Optimal Cytotoxic Therapy for TNBC: *Platinum Agents*

**BRCA1 Cell Lines Exhibit Differential Chemotherapy Sensitivity**

- Increased sensitivity to DNA damaging agents like cisplatin


**Cisplatin As Preoperative Therapy in Patients With BRCA1 Mutations**

- 10 patients with *BRCA1* mutations
- Stage I-III disease
- Treatment:
  - Preoperative Cisplatin 75 mg/m² q 3 weeks x 4
  - Mastectomy
  - AC x 4
- Path CR = No invasive tumor in breast or nodes

Path CR rate = 9/10 = 90%

Brysli T Br Ca Res Treat 2009;115:359
DF/HCC Preoperative Cisplatin in TNBC

> 2cm, Stage III
ER/PR/Her Neg
Research Core Biopsy
N=28

Cisplatin
75mg/m² q3wks
× 4 cycles

SURGERY

Standard Adjuvant Therapy per MD

Pathologic CR 6 (22%)
Clinical CR 4 (14%)
Clinical PR 10 (36%)
Stable Disease 5 (17%)

Silver et al., JCO 2010

Predictors of Response to Pre-operative Cisplatin in TNBC

Refer to subtypes. Cisplatin response.

Rx

Sensitive

Resistant

Shier et al. JCO 2010

Randomized Phase II trial:
Neoadjuvant Cisplatin vs AC
in Women with Newly Diagnosed Breast Cancer and Germline BRCA Mutations

NFORM

Innovations in Management of Breast Cancers, NCISupported Career Awards
Schema
Randomized Phase 2: 166 patients

“Targeting” Triple Negative Breast Cancer

Angiogenesis in TNBC:
Targeting VEGF
Is There a Role for Angiogenesis Inhibition in TNBC?

Pre-operative Cisplatin/Bevacizumab for TNBC

RESULTS
Path CR (Miller-Payne 5) 8/51 = 16%
Almost path CR (Miller-Payne 4) 10/51 = 20%
18/51 = 36%

German Breast Group: addition of bevacizumab to chemotherapy

ECT: 969
ECT-B: 956
Pathological Complete Response (pCR), According to Subgroup.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Odds Ratio (95% CI)</th>
<th>Test for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjacent</td>
<td>505</td>
<td>1.28 (0.82-2.00)</td>
<td>0.26</td>
</tr>
<tr>
<td>Adj.</td>
<td>334</td>
<td>1.73 (0.99-3.07)</td>
<td>0.05</td>
</tr>
<tr>
<td>Age ≥ 70</td>
<td>511</td>
<td>1.27 (0.85-1.93)</td>
<td>0.20</td>
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<tr>
<td>Age ≤ 70</td>
<td>405</td>
<td>1.90 (1.07-3.38)</td>
<td>0.03</td>
</tr>
<tr>
<td>Tumor stage</td>
<td>104</td>
<td>1.50 (0.83-2.71)</td>
<td>0.20</td>
</tr>
<tr>
<td>Size ≤ 2 cm</td>
<td>106</td>
<td>1.28 (0.81-2.03)</td>
<td>0.25</td>
</tr>
<tr>
<td>Size &gt; 2 cm</td>
<td>496</td>
<td>1.26 (0.79-2.04)</td>
<td>0.38</td>
</tr>
<tr>
<td>Lymph node status</td>
<td>708</td>
<td>1.28 (0.70-2.36)</td>
<td>0.41</td>
</tr>
<tr>
<td>No. ≤ 3</td>
<td>792</td>
<td>1.28 (0.71-2.31)</td>
<td>0.45</td>
</tr>
<tr>
<td>No. &gt; 3</td>
<td>400</td>
<td>1.26 (0.65-2.47)</td>
<td>0.53</td>
</tr>
<tr>
<td>Avoidance</td>
<td>708</td>
<td>1.28 (0.71-2.31)</td>
<td>0.45</td>
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<tr>
<td>Surgery</td>
<td>792</td>
<td>1.28 (0.65-2.47)</td>
<td>0.53</td>
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<tr>
<td>Endocrine</td>
<td>505</td>
<td>1.28 (0.82-2.00)</td>
<td>0.26</td>
</tr>
<tr>
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<tr>
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<td>106</td>
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<td>0.25</td>
</tr>
<tr>
<td>3 &amp; 4</td>
<td>496</td>
<td>1.26 (0.79-2.04)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Intergroup/CALGB 40603: Triple Negative Pre-operative Trial (Sikov, PI)

N=400 ER/PR/HER2- Stage II-III B

mTOR-AKT Pathway:
Targeting mTOR
mTOR Is a Central Regulator of Growth and Metabolism


Testing mTOR Inhibitors in Combination Therapy with other p73-Inducing Drugs

DNA Damage → Apoptosis → Tumorigenesis

mTOR Inhibitors

Testing mTOR Inhibitors in Combination Therapy with other p73-Inducing Drugs

p73
p63
actin

Taxol + Cisplatin + mTOR inhibitor = p73 induction, P63 suppression → Apoptosis

(CDDP = Cisplatin; Puma = p73 target gene)
**Vanderbilt: RAD001 Neoadjuvant Study Design**

**Stage II and III triple-negative breast cancer**

- **Arm 1 (2:1)**
  - Breast cancer
  - Surgery
  - Cisplatin + Placebo
  - Cisplatin + Paclitaxel + Placebo

- **Arm 2**
  - Core biopsy
  - Proliferation/apoptosis markers (IHC)
  - Pathway activity markers (IHC)
  - RNA microarrays
  - Ultrasound

Cisplatin 25 mg/m² weekly
Paclitaxel 80 mg/m² weekly

**JAK-STAT Pathway:**

**JAK2 Inhibition**

**Identification of IL6-JAK-STAT Pathway as Relevant in Breast Cancer**

- **Intra-tumoral heterogeneity**
  - CD44+/CD24− cells with stem cell-like characteristics
  - Found in ~70% of luminal, ~50% of HER2+, ~100% of basal-like tumors
  - Associated with poorer outcomes even after controlling for ER status and grade

- **Hypothesis:** Targeting this cell population may be clinically beneficial

Preferential Activation of IL6-JAK2-STAT3 Pathway in Basal-Like BC Cells

IL-6 secreted by basal-like BC cell lines

IL-6 secretion accompanied by elevated pSTAT3 levels

Autocrine growth regulatory loop appears to be interrupted by JAK inhibitor, as demonstrated by reduction of pSTAT3 levels upon treatment

Increased cell density is associated with increased activation of STAT3

Evidence that E-cadherin stimulates IL-6 via Rac1/COB42: activation of JAK2 “autocrine loop”
Importance of JAK2-STAT3 Signaling Pathway in Tumor Growth

Images provided courtesy of Kornelia Polyak, MD, PhD.

Preoperative Treatment with Standard CT + JAK2 Inhibitor (ruxolitinib) in TN IBC

Phase 1: Metastatic BC
- ddAC + ruxolitinib

OR

Weekly paclitaxel + ruxolitinib

Phase 2: Untreated TN IBC
- Biopsy 1
  Cycle 1
  ddAC + ruxolitinib

- Biopsy 2
  Cycle 2
  ddAC + ruxolitinib

- Cycle 3, 4
  ddAC + ruxolitinib

- Weekly paclitaxel x 12 + ruxolitinib

- Biopsy 3
  MRM

Key Questions Concerning TN - LABC

- Are all TNBC alike?
  - Do we need to perform microarray on all breast cancers to understand each patient’s disease?

- How do we choose appropriate chemotherapeutic agents?
  - Do not forget traditional agents in light of newer regimens – current focus on platinum agents.

- Are there other “targets” in TNBC that can be used in directed therapy?
  - Angiogenesis inhibitors – are they best for TNBC?
  - Explore new targets –
    - mTOR inhibitors
    - JAK2 inhibitors
Summary

• The pathologic response to neoadjuvant chemotherapy can be used prognostically in TNBC
• Standard anthracycline/taxane combinations are effective in TNBC
• Current research focus on DNA-damaging agents (platinum) and angiogenesis inhibitors – final analysis is still pending
• Encouraging pre-clinical data supports investigation of other targeting agents: mTOR inhibitors and JAK2 inhibitors