Clinical Trial Strategies for an Uncommon Cancer

Beth Overmoyer MD, FACP
Director, Inflammatory Breast Cancer Program, DFCI

Duke IBC Consortium
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Disclosure

Research Support (Clinical Trial Support)

- Incyte Corp.
- Easai Co.
- Genentech Inc.
The State of IBC Clinical Management

Challenges to Face and Overcome
“Tri-modality” Therapy: Mainstay of Treatment for Inflammatory Breast Cancer

Primary Systemic Therapy

Mastectomy + Axillary LN Dissection

Radiation to Chest Wall and Regional Lymph Nodes

**Challenge #1:** Optimal response to NAS is critical - to maximize the ability to complete TMT

Adjuvant Endocrine Rx (HR+) +/or Trastuzumab / Pertuzumab (HER2+)
Completion of Tri-modality Therapy (TMT): Crucial for Optimal Outcome of IBC

- National Cancer Data Base (NCDB) 1998-2010
  - $N = 10,197$ IBC underwent surgery
  - Median OS: 72 mo (TMT) v 26 mo (surgery alone)
  - 37% improvement in OS among pts treated at academic centers

**Challenge #2**: Convincing patients and physicians to WAIT TO TREAT – until clinical trial options are discussed

<table>
<thead>
<tr>
<th>Modality</th>
<th>5 - yr OS</th>
<th>10 - yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT</td>
<td>55.4%</td>
<td>37.3%</td>
</tr>
<tr>
<td>Chemo + Surgery</td>
<td>42.9%</td>
<td>28.5%</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>NA</td>
<td>16.5%</td>
</tr>
</tbody>
</table>
## Retrospective Studies of Preoperative Chemotherapy for IBC

<table>
<thead>
<tr>
<th></th>
<th>No. IBC</th>
<th>Chemotherapy</th>
<th>RR</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>68</td>
<td>CAF or CEF / CMF</td>
<td>pCR: 3%</td>
<td>4 yr.</td>
</tr>
<tr>
<td>U Penn</td>
<td>52</td>
<td>CMF +/- CAF</td>
<td>pCR: 12%</td>
<td>NR</td>
</tr>
<tr>
<td>France</td>
<td>120</td>
<td>FEC-HD</td>
<td>pCR: 15%</td>
<td>5 yr.</td>
</tr>
<tr>
<td>British Columbia</td>
<td>308</td>
<td>CT v intensive CT (+ T)</td>
<td>pCR: 28% v 33%</td>
<td>3.2 yr.</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>240</td>
<td>FAC v FAC + T</td>
<td>pCR: 10% v 25%</td>
<td>3.4 v 4.3 yr</td>
</tr>
</tbody>
</table>

- Majority of literature is based upon retrospective studies
- NAS varies over time in each study
- Best pCR rate is with anthracycline and taxane regimen
Challenges of Enrolling into IBC-Specific Clinical Trials

1) Clinical signs vary and complicate the diagnosis

2) Rapid onset – 3 months

3) 25-35% incidence of metastasis at diagnosis
Prospective Clinical Trials with Chemotherapy – Outcome ≠ IBC Response

Dose-Dense versus Conventional Preoperative Chemotherapy (AGO-1)

- 668 patients with LABC
- Overall group benefitted from intensive (dd) chemotherapy:
  - Improved pCR – 18% vs 10%
  - Improved time to disease recurrence
  - Improved overall survival

- 100 IBC
- No difference with intensity of chemotherapy:
  - No difference in pCR – 12% vs 10%
  - No difference in time to disease recurrence
  - No difference in overall survival

Untch M JCO 2009; 27:2938
pCR Rates in SWOG 0012: Standard AC versus “Continuous” AC – Differ in IBC

- 356 Overall vs 111 IBC (31%)
- Overall: pCR, DFS, OS – no difference
- Higher pCR in IBC – 27% vs 13% (p=.06)

Georgiana K. Ellis et al. JCO 2011;29:1014-1021
Clinical Trials for IBC: Looking for Therapeutic Targets

Emphasis on Collaboration
HER2: an Exceptional Therapeutic Target for IBC

SEER 2010-2013 (N=403):

- Supports superior survival with HER2+ IBC compared with HER2 negative
- HR = 0.427 (p<0.05)
## NAS with Dual Anti-HER2 Therapy Includes Few HER2+ IBC

### Neospherae

<table>
<thead>
<tr>
<th></th>
<th>T+D (N=107)</th>
<th>T+D+P (N=107)</th>
<th>T+P (N=107)</th>
<th>P+D (N=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBC</td>
<td>7 (7%)</td>
<td>10 (9%)</td>
<td>7 (7%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>tpCR (all)</td>
<td>23 (22%)</td>
<td>42 (40%)</td>
<td>12 (11%)</td>
<td>17 (18%)</td>
</tr>
<tr>
<td>5y -DFS</td>
<td>81%</td>
<td>84%</td>
<td>80%</td>
<td>75%</td>
</tr>
</tbody>
</table>

### Trypheana

<table>
<thead>
<tr>
<th></th>
<th>FEC+HP x 3 → T+HP x 3 (N=73)</th>
<th>FEC x 3 → T+HP x 3 (N=75)</th>
<th>TCH+P x 6 (N=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBC</td>
<td>5 (7%)</td>
<td>4 (5%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>tpCR (all)</td>
<td>41 (56%)</td>
<td>41 (55%)</td>
<td>48 (64%)</td>
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</tbody>
</table>

- NAS with combination pertuzumab-trastuzumab is superior to single anti-HER2 therapy
- Extrapolation of efficacy to IBC is based upon 6-7% enrollment of IBC
Hypothesis:
Can we limit the amount of chemotherapy and maximize the HER2-directed therapy in the treatment of HER2+ IBC?

<table>
<thead>
<tr>
<th>Total pCR (ypT0/Tis , ypN0)</th>
<th>RCB-0 (pCR, ypT0/Tis, ypN0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate = 10/20 pts; %</td>
<td>10</td>
</tr>
<tr>
<td>Rate = 10/18 pts; %</td>
<td>56%</td>
</tr>
</tbody>
</table>

Based upon primary protocol criteria:
Based upon total number of pts having surgery:
Options for Collaboration in Clinical Trials

Translational Breast Cancer Research Consortium (TBCRC)
Investigator-Initiated, Multi-institutional Studies
IBC International Consortium
Identifying Unique Therapeutic Targets in TN-IBC – Cancer Stem Cells

- Inflammatory breast cancer contains a significant component of cells which are CD44+CD24-
- CD44+CD24- cells are often classified as having “stem cell” or “progenitor-like” properties which play a critical role in metastasis and resistance to treatment
- The IL6/JAK2/STAT3 pathway is activated and required for the growth of CD44+CD24- cells in breast cancer

Data courtesy of Kornelia Polyak MD, PhD

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IBC-patient derived xenograft model (PDX) \((right)\) recapitulates the immunoflorescence pattern of primary IBC \((left)\) CD44+CD24-, pSTAT3 positive.

After administration of JAK2 inhibitor to the PDX model, there is suppression of pSTAT3 levels \((right)\) and a significant reduction of % cells expressing pSTAT3 \((left)\).

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Marotta J Clin Invest 2011;121:2723
• Xenograft models of IBC show a synergistic reduction in tumor weight with combined ruxolitinib and paclitaxel

• Close to 100% TN-IBC demonstrate high pSTAT-3 levels

• This supports examining JAK2-STAT3 pathway as a therapeutic target in TN-IBC – TBCRC 039

Data courtesy of Kornelia Polyak MD, PhD and Guillermo Peluffo PhD
TBCRC 039: Phase II Trial of Ruxolitinib and Chemotherapy in TN-IBC

Overmoyer et al SABCS 2017; supported by Incyte Inc. and IBC Research Foundation
There is an identifiable need to focus clinical trial / translational research specifically for IBC

There is a need for academic institutions to join together and collaborate on studies for IBC

Through the efforts of the Translational Breast Cancer Research Consortium, the IBC community has found a partner to help advance the treatment for and understanding of IBC

- TBCRC 039: Ruxolitinib and chemotherapy for TN-IBC
  - DFCI, Duke, Johns Hopkins, Mayo Clinic, MDACC, Univ. Michigan, Univ. Pennsylvania

Involvement with the IBC International Consortium allows for expansion of this collaboration on an international level