Therapeutic Targets for Triple-Negative Breast Cancer: Focus on Platinums and EGFR Inhibition

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Disclosures for Lisa A Carey, MD

No real or apparent conflicts of interest to disclose
Basal-Like Breast Cancer: Biology and Behavior

• Typically high grade, high expression of proliferation genes
• EGFR is a characteristic of the basal gene cluster
• Short RFS in stage I-III (relapse peak 2-3 y)
• Short PFS in stage IV

Is Chemosensitivity General or Drug-Specific? (No one knows, there are arguments for both)

Proliferation Gene Set
(Highly expressed in basal-like breast cancer)

BUB1
PLK1
Thymidylate Synthetase = 5-FU
EZH2
DNA Polymerase alpha
Cyclin A2, B2, E1
Tubulin = taxanes, other antitubulins
BRCA1, 2
MCM2, 3, 5, 6, 7, 8, 10
Forkhead Box M1
MAD2
DHFR = methotrexate
MYBL2
Ki-67
PTTG1
Replication Factor C
CENPA, E, F, H
TOP2a = doxorubicin, etoposide
STK6/15
RAD51
FANCA
PCNA
MSH2
Ribonucleotide reductase = HU
CHEK1
CDC1, 2, 7, 8, 20, 25
Chemosensitivity and TNBC

Pathologic complete response (complete tumor eradication) to preoperative anthracycline-taxane-based chemotherapy:

<table>
<thead>
<tr>
<th></th>
<th>T-FAC¹ (N = 82)</th>
<th>AC-T² (N = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A/B</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Normal-like</td>
<td>0%</td>
<td>NA</td>
</tr>
<tr>
<td>HER2+/ER-</td>
<td>45%</td>
<td>36%</td>
</tr>
<tr>
<td><strong>Basal-like/triple negative</strong></td>
<td><strong>45%</strong></td>
<td><strong>27%</strong></td>
</tr>
</tbody>
</table>

- Basal-like/triple negative breast cancer responds to anthracycline-taxane-based chemotherapy.
- Conventional chemotherapy regimens remain standard of care.

Drug-Specific Chemotherapy for TNBC?

- “BRCAness” of TNBC and sensitivity to DNA damaging agents?
- Platinums classic
- Others, e.g. alkylators?

Adjuvant Choices for TNBC? NCIC-CTG MA.5 Revisited

<table>
<thead>
<tr>
<th>Biologic subtype</th>
<th>CEF</th>
<th></th>
<th>CMF</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>5-year OS</td>
<td>N</td>
<td>5-year OS</td>
<td></td>
</tr>
<tr>
<td>Luminal A</td>
<td>62</td>
<td>93%</td>
<td>71</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Luminal NOS</td>
<td>36</td>
<td>94%</td>
<td>26</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>Luminal B</td>
<td>61</td>
<td>71%</td>
<td>65</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Luminal B (HER2+)</td>
<td>21</td>
<td>71%</td>
<td>27</td>
<td>44%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HER2+/ER-</td>
<td>20</td>
<td>55%</td>
<td>23</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Core Basal</td>
<td>35</td>
<td>51%</td>
<td>35</td>
<td>71%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TNP Non-Basal</td>
<td>9</td>
<td>65%</td>
<td>20</td>
<td>63%</td>
<td></td>
</tr>
</tbody>
</table>

Intriguing, although retrospective and small

## Platinum Sensitivity in BRCA1+/TNBC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pop’n</th>
<th>Regimen</th>
<th>N</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byrski</td>
<td>BRCA1+</td>
<td>Non-platinum</td>
<td>90</td>
<td>14 (16%)</td>
</tr>
<tr>
<td></td>
<td>BRCA1+</td>
<td>CDDP 75mg/m² x 4</td>
<td>12</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>Silver</td>
<td>Sporadic TNBC</td>
<td>CDDP 75mg/m² x 4</td>
<td>28</td>
<td>6 (22%)</td>
</tr>
<tr>
<td></td>
<td>BRCA1+</td>
<td>“ “</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
</tbody>
</table>

- **Neoadjuvant trials:**
  - Retrospective trial suggests exquisite sensitivity in BRCA1+
  - Prospective trial in TNBC less clear
- **Metastatic TNBC:**
  - BALI-1 control arm cisplatin only – 10% RR
Intergroup/CALGB-40603 Triple Negative Neoadjuvant Trial

- **N = 362**
- **ER/PR/HER2-**
- **Stage II-IIIB**

**Paclitaxel ± Carboplatin**

**Dose-dense AC**

**Surgery**

**RT prn**

- Breast imaging
- Blood MUGA
- Tumor biopsy

**Paclitaxel ± Carboplatin**

**Bevacizumab**

**Paclitaxel ± Carboplatin**

Blood

Dose-dense AC

Surgery

RT prn
The basal cluster includes CK 5, 17, EGFR, αB crystallin, c-kit, etc expression.

54%+ by immunostains
Cell lines EGFR dependent

Molecular target?
### EGFR Inhibition in Stage IV Breast Cancer: US Oncology 225200

<table>
<thead>
<tr>
<th></th>
<th>Irinotecan + carboplatin</th>
<th>Irinotecan + carboplatin + cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent trial RR</td>
<td>31%</td>
<td>38%</td>
</tr>
<tr>
<td>TNBC RR (N = 62)</td>
<td>30%</td>
<td>49%</td>
</tr>
<tr>
<td>TNBC PFS</td>
<td>5.1m</td>
<td>4.7m</td>
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- Augmented response rate in TNBC, but no improvement in PFS

EGFR Inhibition in Triple Negative: TBCRC 001

Largely pretreated stage IV TNBC:

<table>
<thead>
<tr>
<th></th>
<th>Cetuximab</th>
<th>Cetuximab + carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>31</td>
<td>71</td>
</tr>
<tr>
<td>Clinical benefit</td>
<td>10%</td>
<td>31%</td>
</tr>
<tr>
<td>Response rate</td>
<td>6%</td>
<td>17%</td>
</tr>
<tr>
<td>PFS</td>
<td>1.4 m</td>
<td>2 m</td>
</tr>
</tbody>
</table>

- Single agent EGFR – low RR, not pursued
- 16 patients allowed serial biopsy of a metastatic lesion → This is how we learn about drug effect and resistance

EGFR Inhibition in Triple Negative: BALI-1

Largely 1st line stage IV:
CDDP 75 mg/m² q3wk x 6 cycles ± cetuximab (usual dose/schedule).
Crossover permitted.

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin + Cetuximab</th>
<th>Cisplatin (CDDP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>115</td>
<td>71</td>
</tr>
<tr>
<td>Response Rate (1° endpt)</td>
<td>20% (13-28%)</td>
<td>10% (4-21%)</td>
</tr>
<tr>
<td>PFS (radiographic)</td>
<td>3.7m (2.8-4.3)</td>
<td>1.5m (1.4-2.8)</td>
</tr>
</tbody>
</table>

- Did not meet RR endpoint (OR 2.9)
- RR doubled, PFS 1.5m → 3.7m
- But poor outcome regardless. Is this active enough?
TBCRC 001: Treatment Effect in Serial Biopsies

Pre-therapy

EGFR expressed

EGFR pathway

EGFR activated

Red = Expressed
Green = Not expressed

Courtesy of Chuck Perou

TBCRC 001: Treatment Effect in Serial Biopsies (cont)

Post-therapy (Cetuximab + Carboplatin x 1 week): CLINICAL RESPONDER

EGFR inactivated by therapy

Non-Response in an EGFR-Activated Tumor

Non-Response in an EGFR-Activated Tumor (cont)

Post-therapy (Cetuximab + Carboplatin x 1 week)

No change with Rx

Summary

• Triple-negative disease has aggressive behavior
  - High proliferation may make it chemosensitive
  - Duration of response typically short
• Preclinical rationale for DNA damaging cytotoxic agents
  - Validity of approach awaits clinical trials
• EGFR is a natural target in basal-like breast cancer
  - Preclinical data consistent
  - Clinical data – activity but not enough
  - Better selection? Single biologic may not suffice.
• Tissue-based studies are key to solving these riddles!