Integrating the New with the Old – Recent Advances in Adjuvant Systemic Treatment Strategies for Breast Cancer

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Cardinal Bernardin Cancer Center

Selected systemic therapy results from San Antonio 2010, St. Gallen 2011, ASCO 2011, and the Oxford Overview for early stage disease

THEMES

• Targeting therapy to subsets defined by biology – standard pathologic criteria and multigene assays
• Neoadjuvant models – 2010-11 advances and controversy
• Status of the “new paradigm” of second generation neoadjuvant consortia studies
• Presurgical window model
• Our greatest challenge

Selected Adjuvant Therapy Clinical Trials 2010-2011 – What’s New from the Oxford Overview and Individual Trial Updates

EBCTCG Anthracyclines vs No Chemo

EBCTCG Anthracyclines vs Anthracyclines

EBCTCG Taxane/Anthra vs Anthracyclines

Postmenopausal, Node+, ER+

S8814 (INT 0100) Disease-Free Survival by Randomized Treatment Group

**Significantly different, P<0.05 by log-rank test**

Years from Registration

Disease-Free Survival (%)

N at risk

Treatment Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Event-free Survival (%)</th>
</tr>
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<tbody>
<tr>
<td>CAF (586)</td>
<td>10-year DFS: 60% (64%, 56%)</td>
</tr>
<tr>
<td>CAF + T (550)</td>
<td>10-year DFS: 60% (64%, 56%)</td>
</tr>
<tr>
<td>T (361)</td>
<td>10-year DFS: 30% (34%, 26%)</td>
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EBCTCG chemotherapy update, 2010-2011

Not for publication or citation, manuscript in preparation
Subgroup Analyses of DFS among Patients with Central Pathology Review: No Benefit to TAC if HER2+ (any ER)

Targeting Therapy to Subsets Defined by Biology – St. Gallen 2011, Standard Pathologic Criteria and Multigene Assays

Breast Cancer Subtypes

PAM50 Intrinsic Subtypes Present and Clinically Significant for Prognosis within both ER+ and ER- Tumors, with Heterogeneity in HER2+(clinical) Group (N0, no systemic adjuvant treatment)
St. Gallen 2011: “Shorthand” Determination of Breast Cancer Subtypes

Intrinsic Subtype | Surrogate Definition
---|---
Luminal A | ER and/or PgR(+) and HER2(-)
Luminal B1 | ER and/or PgR(+), HER2(-) Ki67 low (<14%)
Luminal B2 | ER and/or PgR(+), HER2(-) Ki67 high
HER2 over-expression | ER and/or PgR(-), HER2(+) basal-like

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<th>Notes</th>
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<td>Endocrine therapy alone</td>
<td>Few require cytotoxic (e.g. high nodal status).</td>
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<td>HER2 positive (non luminal)</td>
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<td>Patients at very low risk may be observed without treatment.</td>
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<td>Triple negative (ductal)</td>
<td>Cytotoxics</td>
<td>Lacks cyclin D1 overexpression.</td>
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<td>Special histological types **</td>
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S8814 CAFT vs T Node Positive Breast Cancer Specific Survival by RS

Interaction p = 0.021
**S1007 “RxPONDER” Launched January, 2011**

(Medical Oncology Investigators: Gonzalez-Angulo A-M, PI; Hortobagyi G; Albain K)

**NSABP B-47**

Evaluating Trastuzumab Efficacy across Low HER2 Levels

**New Data Forthcoming from NSABP**

- HER2-trastuzumab interaction is modulated by ER level
- A 10 gene-based predictive model being validated to identify who does not benefit from trastuzumab
- HER2 negative patients (especially triple negative) may benefit from trastuzumab

*Presented by S. Paik in closed session, not yet public domain*

**ADJUVANT CHEMOTHERAPY – Improving on Anthracycline Benefit by “Metronomic” Schedule?**

**S0221: Updated Interim Analysis: Anthracycline Question**

Disease-Free Survival by Delivery of AC

- 5-year DFS: AC weekly 79% vs. AC q 2 wk 82%
- HR = 1.15 (95% CI 0.95 - 1.41) AC weekly vs. AC q 2 wk

**S0221: Revised Schema for Remaining 534 Patients**

- Desorubicin 60 mg/m2 Cyclophosphamide 600 mg/m2
  Peg-filgrastim q 2 weeks x 4
- Paclitaxel 175 mg/m2 Peg-filgrastim
  q 2 wks x 6

- Desorubicin 60 mg/m2 Cyclophosphamide 600 mg/m2
  Peg-filgrastim q 2 weeks x 4
- Paclitaxel 80 mg/m2 Weekly x 12
On Abandoning Adjuvant Anthracyclines?

Time Trends in Type of Chemotherapy: Medicare Cohort: Patients 66+ (N=5511)

Time Trends in Type of Chemotherapy: Private Insurance Cohort: Patients <65 (N=30,658)

Insights

- Use of anthracycline-based chemotherapy has fallen dramatically
- Due to “TC enthusiasm”
- Will we see rise in BC mortality down the road?
- See thoughtful and comprehensive review of this topic by Dr. I. Craig Henderson in Oncology, February 2011

3 New Studies on More Adjuvant Chemotherapy – Can We Add to the A-C-T Backbone?

FinXX Overall Survival

HR = 0.73 (95% CI: 0.52 – 1.04)

P = 0.080
Conclusions “Addition” Trials

- Toxicities not insignificant when 4th drug added
- Exploratory analyses in 2 studies showed benefit to adjuvant capecitabine in triple negative
- No data to support adding 4th drug to A/C/T backbone in clinical practice
- Could inclusion of patients with indolent, ER+ disease mask a stronger signal for the additional drug?
**NSABP B-40**

**Pathologic Complete Responses (Breast and Nodes)**

- **Endpoints:** pCR, cCR, DFS, gene expression patterns.

- **Operable Breast Cancer:**
  - Tissue for Biomarkers:
    - EC
    - EC+Bev
    - R
    - Operable
  - Surgery
  - +/- Bev

- **Summary Bevacizumab Trials:**
  - Not Ready for Clinical Use
  - Disappointing results overall in 2 trials to date, with discordant results in subsets
  - Impact on OS and DFS unknown
  - Await long-term follow-up of these 2 trials, plus others recently completed/in progress (BETH, BEATRICE, SWOG, E5103, B-46)
  - Need biomarkers to tailor therapy
Promise and Controversies Regarding the Neoadjuvant Approach

- Can rapidly determine tumor response using pCR as the primary endpoint
- Patients who achieve a pCR have better outcomes
- However, in large phase III trials in “all comers” (unselected for a target), regimens with higher pCR rates did not achieve better overall DFS and OS, the gold standards for FDA drug approval
- Need to target new neoadjuvant strategies to biologic subsets that otherwise would not have achieved a pCR without the new agent (eg: the NOAH trial – overall survival predicted by pCR)

NOAH Trial: Preoperative Chemo +/- Trastuzumab for LABC

Path CR Breast/Nodes

<table>
<thead>
<tr>
<th>Chemo + trast</th>
<th>Chemo only</th>
</tr>
</thead>
<tbody>
<tr>
<td>38%</td>
<td>19%</td>
</tr>
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</table>

Gianni L, et al; Lancet 2010

Anti-HER2 therapies: single (a, b, c, e) or dual (a+b, a+e, b+c) blockade

Three New Neoadjuvant Trials HER2+
Presented at SABCS 2010

NeoSphere: pCR Rates Doubled by Dual HER2 Blockade plus Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Trast – Docetaxel</th>
<th>Pertuz - Docetaxel</th>
<th>Trast - Pertuz</th>
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</tr>
</thead>
<tbody>
<tr>
<td>ITT (Overall)</td>
<td>29%</td>
<td>24%</td>
<td>46%</td>
<td>17%</td>
</tr>
<tr>
<td>ER-</td>
<td>37%</td>
<td>30%</td>
<td>63%</td>
<td>27%</td>
</tr>
<tr>
<td>ER+</td>
<td>20%</td>
<td>17%</td>
<td>26%</td>
<td>6%</td>
</tr>
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NeoSphere: pCR Rates Intriguing in Non-Chemotherapy Arm, Especially ER-
Pathologic Response in NeoALTTO
Best if Dual Blockade plus Paclitaxel

<table>
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<tr>
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<th>Path CR (breast only)</th>
<th>Path CR (breast and LN)</th>
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<tr>
<td>Lapatinib + Paclitaxel</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>Trastuzumab + paclitaxel</td>
<td>29%</td>
<td>28%</td>
</tr>
<tr>
<td>Trast + Lap + paclitaxel</td>
<td>51%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Lapatinib + Paclitaxel

Trastuzumab + paclitaxel

Trast + Lap + paclitaxel

Baselga, et al. PSABCS 2010

Inability to give planned doses of lapatinib ~35% in both studies

Neoadjuvant HER2+
ASCO 2011

Guarneri, V (Cher-Lob)
Abstract 507

Holmes, FA (US Oncology)
Abstract 506

CT: wP x 12 → FEC x 4
CT: FEC x 4 → wP x 12

R + T + L (1000-1500)
R + T + L (1500-2000)

24wks
26wks

N=121/115 (recruited/analyzed)
N=100/78 (recruited/analyzed)

Efficacy
(pCR = ypT0/is ypN0)

Guarneri, V Holmes, FA

TBCRC 006: Neoadjuvant Lapatinib & Trastuzumab Without Chemotherapy

Lapatinib (1000 mg/day)

Trastuzumab (4 mg/kg load, 2 mg/kg qw)

(Endocrine Therapy Added if ER++)

Bx

Weeks

n=66 recruited /61 analyzed

pCR ER(-) 46% ER(+) 21%

Chang J, ASCO 2011, Abst. 505

Current Status of a “New Paradigm” of Second Generation Neoadjuvant Consortia Studies which “Build In” Prospective Translational Biologic Questions – NeoBIG and I-SPY2

Guarneri, V et al. ASCO 2011 Abst. 507
Holmes, FA et al. ASCO 2011 Abst. 506

Slide courtesy G. Von Minckwitz
**NEO-ALTTO (reported SABCS 2010)**

450 women with HER2 positive BC (> 2cm)

**ALTTO Met accrual goals Spring, 2011**

**VALIDATION**

Surogate of long-term efficacy

Biomarkers of efficacy/resistance

**I-SPY2 TRIAL**

OPENED FOR ACCRUAL IN 2010

**Summary of I-SPY2 Study Plan**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Agent Chaperone</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figitumubum* (CP-751,071)</td>
<td>IGF1R Inhibitor</td>
<td>Dr. Doug Yee</td>
<td>University of Minnesota</td>
</tr>
<tr>
<td>Neratinib (HKI-272)</td>
<td>Pan ErbB Inhibitor</td>
<td>Dr. John Park</td>
<td>University of California, San Francisco</td>
</tr>
<tr>
<td>ABT-888</td>
<td>PARP Inhibitor</td>
<td>Dr. Hope Rugo</td>
<td>University of California, San Francisco</td>
</tr>
<tr>
<td>AMG 386</td>
<td>Angiogenesis Inhibitor</td>
<td>Dr. Kathy Albin</td>
<td>Loyola University</td>
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* Figitumubum was just withdrawn and will not be available for randomization.

**CHALLENGES**

- Efficient test of multiple promising new agents
- Maintain standard curative therapy... or replace entirely by new agents at some point in the trial
- Identify who can avoid chemotherapy altogether
- Shrinking eligible patient pool due to frequency of the target as well as competing trials with exciting new therapies for one target, and many companies making the “same” drug/target
Use of the Presurgical Window Model to Screen New Agent Activity

Presurgical Window Approach for New Drug/Target Assessment in Early Breast Cancer – What This Model Is and What It’s Not

- Can use small number patients since endpoint is biomarker modulation only - NOT an efficacy trial
- Short time window, not standard neoadjuvant duration
- Thus, can justify new agents alone, since definitive surgery and standard adjuvant recommendations will follow shortly
- Challenges for patient acceptance (extra biopsies, short delay in surgery)
- Requires multidisciplinary buy-in prior to a standard surgical approach

Targeting Critical Cancer Cell Survival Pathways to Overcome Resistance to Standard Endocrine Treatment

- Breast tumor initiating cells (breast cancer stem cells) use Notch receptors/ligands with other pathways for self renewal, resulting in tumor proliferation and progression
- We showed that Notch inhibition with novel compounds - gamma secretase inhibitors (GSI) - potentiates the effects of tamoxifen in xenografts (Rizzo et al. Cancer Research, 2008)
- It is unknown whether GSI plus endocrine therapy result in modulation of Notch and other proliferation markers in human breast cancer
- The “presurgical window setting” is an ideal model to test this hypothesis

Working Hypothesis
Endocrine Therapy + Gamma Secretase Inhibitor - A potential anti-tumor initiating cell effect and a role in overcoming endocrine resistance

Integrating New Agents with Standard, Curative-Intent Therapy in Early Breast Cancer

Conclusions

- We have come a long way with standard chemotherapy and endocrine therapy in phase III adjuvant clinical trial design, improving breast cancer mortality
- Biomarker correlative translational studies yielded refinement in who can avoid chemotherapy
- Neoadjuvant therapy designs need to select for relevant biology if they are to yield strategies that increase cures
- Early excitement with dual HER2 blockade
- The presurgical window model can be used to determine which new targeted therapies merit more expanded neoadjuvant trials