Developing Personalized Therapy Early Breast Cancer: Where are We Now and Where are We Heading?

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Breast Cancer: Background

- Leading cause of cancer for women
  - Over 230,000 cases in US for 2013
  - Represents 29% of new cancer cases
  - Nearly 90% present with local disease
- Second leading cause of cancer death
- Biology is main driver of treatment
- Goal is to provide a more tailored individualized approach by targeting dysregulated pathways

Multimodal Treatment

- **Cut it Out**
  - Surgery: lumpectomy vs mastectomy

- **Nuke it**
  - Radiation

- **Poison it**
  - Chemotherapy (Neoadjuvant=before surgery; Adjuvant=after surgery)
  - Hormonal (Tamoxifen vs. Aromatase Inhibitors)
Breast Cancer Staging

**Stage IA Breast Cancer**
- Tumor is 2 cm or smaller
  - 2 cm
- Cancer in 1 to 3 lymph nodes in the axilla or near the breastbone

**Stage IIA Breast Cancer**
- Tumor is 2 cm or smaller
  - 2 cm
- Breastbone
- Lymph nodes in the axilla

**Stage IIIB Breast Cancer**
- Tumor is larger than 5 cm
  - 5 cm
- Lymph nodes in the axilla
- Inflammatory breast cancer
- Breastbone
Stage III C Breast Cancer

1. Cancer in 10 or more lymph nodes in the axilla
2. Cancer in lymph nodes above or below the collarbone
3. Cancer in lymph nodes in the axilla and near the breastbone

No tumor or tumor is any size
What’s Important

- Age (mean 61yo) and general health
- Tumor size and grade (1-3)
- Lymph nodes
- ER/PR status
- HER2 status
Outcomes of Adjuvant Chemotherapy in Breast Cancer

All patients with the same diagnosis

No Benefit No Toxicity

+ Benefit No Toxicity

+ Benefit + Toxicity

No Benefit + Toxicity

Walgren et al. JCO 2005;23:7342-7349
Objectives

- Case: Chemotherapy or hormonal therapy
- Who should receive chemotherapy?
- The birth of gene-expression signatures
  - Molecular subtypes
- Differences in approach for HR+ vs HR- tumors
- Clinical and economic impact of gene expression profiling
- New targeted drugs, what’s the implication?
Clinical Case

62 y/o WF with newly diagnosed R breast cancer

- **MMG / Ultrasound** → 1.2 x 1.2 cm mass at 10 o’clock + surrounding microcalcifications + several suspicious axillary LNs
- s/p modified radical mastectomy
- **Surgical Path** – 2.1 cm lesion consisting of IDC mixed with DCIS; intermediate grade; 11 (-) LNs; ER+/PR+/HER-2-; T2N0M0
- What is her risk of recurrence?
- What is her risk of death?
- What is the recommendation for adjuvant therapy?
  - Tamoxifen
  - Aromatase Inhibitor
  - Hormonal therapy + chemotherapy
Who Should Receive Adjuvant Chemotherapy?

- 65% of women with invasive breast cancer have LN(-) disease
- Neo/Adjuvant chemotherapy improves decreases relapse and improves survival
- Trials showed the benefit of tamoxifen & chemo in early breast cancer (stage I-II)
  - Likelihood of distant metastases at 10 years is about 15%
  - 85% of pts are OVER treated if chemo given to all patients
- Can we better ID these 15% who’d benefit the most?
- Main clinical prognostic factors: age, tumor size, axillary LN status, tumor histology, grade, and hormone-receptor status

How else can we classify these tumors?
Intrinsic Breast Cancer Subtypes described by Perou et al.

- **Luminal A**
- **Luminal B**
- **HER2+**
- **Basal-like**

<table>
<thead>
<tr>
<th>Pathological Variables</th>
<th>Basal-like (%)</th>
<th>Luminal A (%)</th>
<th>Luminal B (%)</th>
<th>HER2-like (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-positive (IHC)</td>
<td>10</td>
<td>12</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>ER-positive (IHC)</td>
<td>12</td>
<td>96</td>
<td>97</td>
<td>46</td>
</tr>
<tr>
<td>Grade III</td>
<td>84</td>
<td>19</td>
<td>53</td>
<td>74</td>
</tr>
<tr>
<td>Tumor size &gt;2 cm</td>
<td>75</td>
<td>53</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>Node-positive</td>
<td>40</td>
<td>52</td>
<td>65</td>
<td>66</td>
</tr>
</tbody>
</table>

Clinical Outcome Associated with Intrinsic Sub-Types

Luminal tumors have a favorable OS and RFS

Basal and ERBB2 tumors have poor OS and RFS

Gene Expression Profiles or “Signatures”

- Composed of a selection of genes felt to provide prognostic or predictive information about tumors
- A number of gene expression signatures have been developed to help identify those patients at low or high risk for recurrence
- May avoid chemotherapy administration to patients at low risk or patients who will likely not benefit from treatment
The 70-gene Assay: MammaPrint
Mammmaprint: Development of the 70-Gene Signature

- DNA microarray analysis of 78 breast primary tumors (untreated)
  - Pts were <55 years of age with T1-2/N0 disease
  - Pts selected based on outcome: *Distant metastases within 5 years*
- Statistical analysis identified 231 genes correlated with disease outcome → Top 70 genes selected
- Genes that regulate cell cycle, invasion, metastasis, & angiogenesis
- Patients categorized as “good prognosis” or “poor prognosis.”
- Found to be a better predictor of distant metastases within 5 years than all clinical variables in this study (15x BETTER prognosticator)

Retrospective Validation of the 70-Gene Signature

- 295 women ages ≤ 52 with T1-2, LN-/+ breast cancer
  - 226 ER+ / 69 ER-
  - chemo 31%; hormonal 7%; both 7%
- 61 pts included in the analysis were used to develop 70-gene signature

Prognosis Signature Predictive of End Points (10 years)

Probability of Remaining Metastasis-free

- Good signature: 85% ± 4.3%
- Poor signature: 51% ± 4.5%

Overall Survival

- Good signature: 95% ± 2.6%
- Poor signature: 55% ± 4.4%

The 21-gene Recurrence Score: Oncotype DX
Oncotype Dx: The 21-Gene Assay

- Designed to quantify the risk of distant recurrence in patients with ER(+) tumors receiving tamoxifen
- RT-PCR based
- 250 candidate genes selected based on published literature, genomic databases, & experiments based on DNA arrays on fresh-frozen tissue
- Analyzed data from 3 studies (447 patients) to test relation b/w 250 genes and recurrence of breast cancer
- From these studies, 16 genes (+5 reference genes) were selected that correlated with proliferation and endocrine response
Prospective Validation Study of 21-Gene Assay

- Analyzed tumor blocks of 668 patients on NSABP trial B-14 study that were randomized to tamoxifen
- RS was significantly correlated with relapse free interval & OS (p<0.001)
- Rate of distant recurrence at 10 years:
  - **Low risk** – 6.8%
  - **Intermediate risk** – 14.3%
  - **High risk** – 30.5% (similar risk to LN+ patients)

Distant Recurrence as a Function of RS

The likelihood of distant recurrence ↑ continuously as the RS ↑

Kaplan-Meier Plots for Distant Recurrence

All patients

Low Risk RS <18

Intermediate Risk RS 18-30

High Risk RS ≥ 31

Relative & Absolute Benefit of Chemotherapy as a Function of RS

Low RS $\rightarrow$ mean absolute decrease in distant recurrence rate of -1.1%

Intermediate RS $\rightarrow$ no substantial benefit,
But the uncertainty in the estimate cannot Exclude a clinically important benefit

High RS $\rightarrow$ mean absolute decrease in Distant recurrence rate of 27.6%

How Often Does the Recurrence Score Affect Treatment?

- Change in treatment recommendation by oncologist: 31%
  - CHT to HT 23%
- Change in treatment decision by patient: 27%
  - CHT to HT 10%

Is the Recurrence Score Assay Cost Effective?

Prospective Validation of Oncotype DX: The TAILORX Trial

11,248 ER+/LN- patients

Low RS: Hormonal Therapy

High RS: Chemo + Hormonal Therapy

Hormonal Therapy

Chemo + Hormonal

5 Gene Signatures Compared
All models *except* the two-gene ratio model were significant predictors of both RFS and OS.
The Molecular Portrait Hypothesis

You can recognize the Mona Lisa by her smile and her nose and her eyes and even her hands – if you are really good, but not the sky or the trees
Figure 1a.

Clinical Case

62 y/o WF with newly diagnosed IDC R breast

- **MMG / Ultrasound** → 1.2 x 1.2 cm mass at 10 o’clock + surrounding microcalcifications + several suspicious axillary LNs
- s/p modified radical mastectomy
- **Surgical Path** – 2.1 cm lesion consisting of IDC mixed with DCIS; intermediate grade; 11 (-) LNs; **ER+/PR+/HER-2-**; T2N0M0
- **Oncotype DX** - -> *low risk for recurrence*
- Based on oncotype results adjuvant aromatase inhibitor x 5-10 years without chemotherapy
- Zometa 4mg IV q6mo x 5 years also recommended
Hormonal Agents in Breast Ca

- **Tamoxifen**
  - Reduces recurrence by ~30%
  - Hot Flashes, DVT, Uterine Cancer
  - Improves Bone Density, lipid lowering
- **Aromatase Inhibitors (Femara, Arimidex, Aromasin)**
  - Reduces recurrence by 30-40%
  - Arthralgias, Depression, Osteopenia
- **Treatment is usually 5-10yrs**
- **Zometa**
  - Decreases skeletal mets
  - Improved survival by 20-25%
- **Metformin and Statins may have a role**
  - Decrease inflammation, Insulin-growth factor and oncogenesis
Chemotherapy for Breast Cancer

- **AC (adriamycin, cytoxan)**
  - CHF, leukemia, hemorrhagic cystitis
- **Taxanes (taxol, taxotere, abraxane)**
  - neuropathy
- **Platinums (Carboplatin, cisplatin)**
  - Renal Failure, hearing loss
- **Treatment is usually 3-6 months**
- **Herceptin (for HER2+ breast cancer)**
  - CHF
  - Treatment duration = 1 yr
- **Monitoring is typically 5-10yrs**
  - Q3-6mo x first 2-3yrs
  - Q6mo after that
  - ~85% recurrences happen w/in 1st 5yrs
The Promise of Personalized Medicine in Breast Cancer

- **Postmenopausal Women with HR+ breast Cancer**
- **Biologic agents**
  - Her2, EGFR, VEGF, Parp
- **Chemotherapy**
  - Anth, Taxane, Platinum
- **Aromatase Inhibitor**
- **Tamoxifen**
Conclusions, Part 1

- Gene signatures augment current clinicopathological variables in assessing risk of recurrence
- Gene expression profiles may be both prognostic and predictive for patients with early ER/PR positive breast cancer
- What to do with HER2+ and hormone negative tumors?
HER2+ and Triple Negative Cancers are Aggressive

- 15-20% of breast cancer, for each subtype
- Present with more advanced stage
- Historically ~ 50% relapse, usually w/in 3yrs
- Biology not size, drives behavior
- Early/Neoadjuvant Chemotherapy makes sense
  - Can we have tumor “melt away” = pathologically no residual cancer left (pCR, pathologic Complete Response)
# The Response to Neoadjuvant CT Varies in the Different Molecular Subtypes

<table>
<thead>
<tr>
<th>Molecular Subtype</th>
<th>Straver(^1)</th>
<th>Somlo(^2)</th>
<th>Hess(^3)</th>
<th>Total</th>
<th>pCR</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal-type/MP Low Risk</td>
<td>21</td>
<td>0</td>
<td>14</td>
<td>29</td>
<td>1</td>
<td>64</td>
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<tr>
<td>Luminal-type/MP High Risk</td>
<td>67</td>
<td>3</td>
<td>16</td>
<td>53</td>
<td>6</td>
<td>136</td>
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<tr>
<td>HER2-type</td>
<td>41</td>
<td>13</td>
<td>18</td>
<td>24</td>
<td>12</td>
<td>83</td>
</tr>
<tr>
<td>Basal-type</td>
<td>38</td>
<td>13</td>
<td>20</td>
<td>27</td>
<td>15</td>
<td>85</td>
</tr>
</tbody>
</table>

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2. Somlo et al. ASCO, 2009
Association of pCR on EFS and OS

Event-free Survival

HR = 0.48, P* < 0.001

Overall Survival

HR = 0.36, P* < 0.001

pCR (n = 2131)
no pCR (n = 9824)
Target: HER Family
Dual Targeting

Trastuzumab (Herceptin)

Pertuzumab (Perjeta)

ErbB1

HER2/ErbB2

ErbB1

ErbB2

ErbB2

ErbB3

L = Lapatinib.

Downstream signaling pathways

Cell proliferation

Cell survival
pCR Rates by Tumor Subtypes

- **Dual HER2 Blockade**
  - No Tras: 18
  - Yes Tras: 50
  - No Tras: 31
  - Yes Tras: 63

- **HR+**
  - Grade 1-2: 7
  - Grade 3: 16

- **HER2+ HR+**
  - No Tras: 18
  - Yes Tras: 50

- **HER2+ HR-**
  - No Tras: 31
  - Yes Tras: 63

- **TRIPLE NEG**
  - No Tras: 34
What’s Next for HER2: New Agents?

- Trastuzumab-DM1
- HSP90 inhibitors
- HER3 antibodies
- PI3K inhibitors
- Neratinib
Target: TripleNegatives
Poly (ADP-Ribose) Polymerase (PARP) as a Target

- Key regulator of DNA damage repair
  - Involved in DNA base-excision repair
- Binds directly to DNA damage and produces large branched chains of poly(ADP-ribose)
- It is differentially upregulated in primary breast cancers, including the ER-, PR-, and HER2-negative subtype

Mechanisms of Synthetic Lethality-PARP-1

Image from: Iglehart JD, Silver DP. Synthetic Lethality-A new direction in cancer-drug development. NEJM 2009; 361 (2) ; 189-191. © 2009 Massachusetts Medical Society. All rights reserved. Permission requested.
pCR Rates by Tumor Subtypes

Dual HER2 Blockade

Grade 1-2: HR+ - 7, Grade 3: HR+ - 16
No Tras: HER2+ HR+ - 18, Yes Tras: HER2+ HR+ - 50
No Tras: HER2+ HR- - 31, Yes Tras: HER2+ HR- - 63
with Carbo: 60

TRIPLE NEG
Target: The Future
Moving Forward: Novel Targets, Novel Mechanisms

- PI3K / Akt / mTOR pathway inhibitors
- PARP inhibitors
- Src-family TKIs
- HSP90 inhibitors
- Hedgehog, Wnt, Notch, signal inhibitors (CSC)
- Others
Compounds

- Olaparib (Astra Zeneca) po
- Veliparib (ABT888 - Abbot) po
- MK-4827 po
- Iniparib (BSI 201 – Sanofi-Aventis) iv
- AGO 14699 (Pfizer) iv
- INO 1001 (Inotek – Genentech/Roche)
- CEP 9722 (Cephalon)
Figure 1a.

Next-Generation Sequencing (NGS)

- Newer technology which allows for the simultaneous sequencing of hundreds of millions of DNA molecules.
1) DNA/RNA extraction: Extensive optimization
2) LC, Hybrid Capture: Extensive optimization
3) Analysis pipeline: Advanced computational biology
4) Clinical report: Resource intensive

Pre-Analytic Process (Pre-Sequencing)

Post-Analytic Process (Post-Sequencing)

14-17 Day Turnaround Time (From Receipt of Specimen)
82% of cases have “actionable” findings

On average (mean), 3-4 reportable alterations; 1.6 actionable alterations per sample

**Definition of Actionability:**
1. FDA approved targeted therapy in tumor type
2. FDA approved targeted therapy in another tumor type
3. Open clinical trial for which alteration confers trial eligibility

Dataset: First 3,936 qualifying clinical specimens in FMI CLIA lab.
Most Frequently Altered Genes

62/155 most commonly altered genes displayed
76.4% of specimens harbored ≥1 actionable alteration

The “Long Tail” Phenomenon

Oncol 31, 2013 (suppl; abstr 11020)
Targeted Therapies in Cancer Care

VEMURAFENIB
Selective inhibitor of “mutant” BRAF

Before

15 days after

Courtesy of Dr. Grant McArthur
Conclusions, Part 2

- Clearly biology drives disease
- Molecular Profiles are helpful in helping us decide when to give chemo, but not necessary *which* chemo
- With early (preferably neoadjuvant chemorx) HER2+, triple neg, and LN+ Breast cancer can improve survival 2-3x fold
  - These pts would greatly benefit from a pre-operative evaluation
- Individualized, tumor-specific treatment are coming within 5-10yrs
- Thank You!
- Questions?