Updates in Breast Cancer

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Overview

• Operable (Stage I, II or III) Breast Cancer
  • Can some patients forego chemotherapy?
  • Is “more” better?
    • Are 2 HER2-directed drugs better than 1?
    • Are 4 chemotherapy drugs better than 3?
    • Is 10 years of endocrine therapy better than 5?

• Concerns Regarding the Model of Cancer Survivor Care
Operable (Stage I - III) Breast Cancer
Can some patients forego chemotherapy?
Effect of Adjuvant Chemotherapy Therapy on Survival

Never recur

Benefit

Recur with tx

Individualizing Patient Care for Early-Stage Breast Cancer

Patient A
- 63 years old, good health
- 2.0 cm tumor
- 0 positive lymph nodes
- Estrogen receptor positive

Patient B
- 63 years old, good health
- 2.0 cm tumor
- 0 positive lymph nodes
- Estrogen receptor positive

Low Risk

High Risk
Oncotype Dx® Recurrence Score is Prognostic

Oncotype DX® Predicts Chemotherapy Benefit

Study Schema the TAILORx Trial

Node-Neg, ER-Pos Breast Cancer

Oncotype DX® Assay

RS ≤10
Hormone Therapy

RS 11-25
Randomize Hormone vs Chemotherapy + Hormone

RS >25
Chemotherapy + Hormone

Primary study group

To determine whether adjuvant hormonal therapy is *not inferior* to adjuvant chemohormonal for patients in the “primary study group”
Low Risk Patients Can Forego Chemotherapy

Prospective Validation of the 21 Gene Recurrence Score: 1626 patients with a recurrence score of 0 to 10.

Operable (Stage I - III) Breast Cancer
Is “more” HER2-directed therapy better for HER2+ disease?
NeOAdjuvant Herceptin (NOAH) Study

- Locally advanced breast cancer, HER2+, n=235

The Addition of Herceptin to Chemotherapy Improves pCR and Survival

Breast cancer event free survival and overall survival were significantly improved by the addition of Herceptin to Chemotherapy.

- Chemo + trastuzumab
- Chemo only

pCR in breast and LNs

p = 0.001

Pertuzumab Mechanism of Action

By blocking HER2 dimerization, pertuzumab inhibits key HER signaling pathways that mediate cancer cell proliferation and survival\textsuperscript{1-4} Pertuzumab prevents the formation of HER2:HER3 receptor pairs\textsuperscript{1,5}

Dual HER2-directed Neoadjuvant Therapy

- Herceptin (H) alone or combined with Perjeta (P)

<table>
<thead>
<tr>
<th>Chemotherapy + HER2-directed Therapy</th>
<th>pCR Rate Breast and LNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NeoSphere (^1) (N = 417)</td>
<td></td>
</tr>
<tr>
<td>(T_{\text{doc}}) H</td>
<td>22%</td>
</tr>
<tr>
<td>(T_{\text{doc}}) P</td>
<td>18%</td>
</tr>
<tr>
<td>(T_{\text{doc}}) H+P</td>
<td>39%</td>
</tr>
<tr>
<td>None</td>
<td>11%</td>
</tr>
</tbody>
</table>

\(^1\) Gianni et al, Lancet Oncol 2012
Dual HER2-directed Therapy

• We await the results of the APHINITY trial to evaluate the benefit of *adjuvant* pertuzumab in combination with trastuzumab

• In the interim…
  • Pertuzumab granted accelerated FDA-approval on 30 Sept 2013
Operable (Stage I - III) Breast Cancer
Is “more” chemotherapy better for ER/HER2-disease?
Does the Addition Carboplatin to Standard AC-Taxol Chemotherapy Improve Outcomes?

Key Eligibility: Clinical stage II or III breast cancer, ER and PR ≤ 10%

Sikov et al, J Clin Oncol. 2014 Aug 4
Carboplatin Increases the pCR

Sikov et al, J Clin Oncol. 2014 Aug 4
Impact of Carboplatin on EFS and OS is Marginal

Sikov et al, SABCS 2015 Abstract
Carboplatin for TNBC: Unanswered Questions

- A similar German study did show that the addition of Carboplatin increased pCR, as well as EFS and OS

- Should all patients with TNBC get Carbo as part of their treatment plan?

- How can we avoid overtreating the ~40% of patients destined to have a pCR without Carbo?
Operable (Stage I - III) Breast Cancer
Is “more” endocrine therapy better for ER+/HER2- postmenopausal disease?
MA.17R Trial Schema and Design

AI x 5 yrs - Following Prior 5 years of AI - preceded or not by Tamoxifen

Any duration of prior Tamoxifen  
4.5-6 yrs of Aromatase Inhibitor  
Letrozole 2.5 mg po od  
Letrozole 2.5 mg po od

RANDOMIZE

n = 1918  
Letrozole 2.5 mg po od  
Placebo  
5 yrs
Does extending aromatase inhibitor therapy from 5 to 10 years improve patient outcomes?

As compared to the standard of 5 years of letrozole (Femara), 10 years reduces the risk of breast cancer relapse or a new breast cancer in the opposite breast by 34%.
10 Years is More Effective than 5 Years of Endocrine Therapy for DFS
Patient Survival at 5 Years Follow-up is the Same

5-year OS: 93% LET vs. 94% PLAC

- Letrozole
- Placebo

Years
## Impact on Breast Cancer Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Letrozole N = 959</th>
<th>Placebo N = 959</th>
<th>Absolute Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any relapse or new breast cancer</td>
<td>67 (7.0%)</td>
<td>98 (10.2%)</td>
<td>3.2%</td>
</tr>
<tr>
<td>Local relapse in breast or lymph nodes</td>
<td>19</td>
<td>30</td>
<td>1.1%</td>
</tr>
<tr>
<td>New breast cancer (opposite breast)</td>
<td>13</td>
<td>31</td>
<td>1.8%</td>
</tr>
<tr>
<td>Distant (metastatic) relapse</td>
<td>42</td>
<td>53</td>
<td>1.1%</td>
</tr>
</tbody>
</table>
Toxicities

- Patients taking the letrozole (compared to placebo) experienced
  - More musculoskeletal pain
    - 18% v. 14% in placebo
  - More bone fractures
    - 14% v. 9% in placebo
  - More new diagnoses of osteoporosis
    - 11% v. 6% in placebo
  - No compromise to quality of life measures
    - Menopausal symptoms
    - Physical function
    - Mental function
Concerns Regarding the Model of Cancer Survivor Care
Why should you care about the model by which healthcare is delivered to cancer survivors?
Estimated Numbers of U.S. Cancer Survivors by Site

There will be a projected 26% increase in the number of female survivors and 36% increase in male survivors between 2014 – 2024.

Source: Data Modeling Branch, Division of Cancer Control and Population Sciences, National Cancer Institute.

Cancer Survivor Prevalence by Age

There is a booming population of cancer survivors $\geq 65$ years of age
Our Challenges

- Aging population
  - Breast cancer incidence projected to increase by ~45% by 2030

- Survival rates improving
  - Across all stages of disease, ~90% of women alive at 5 years

- Projected shortage of oncologists by 2025
The Current Breast Cancer Survivor Care Model

- Patient completes definitive locoregional therapy +/- chemotherapy/HER2-directed therapy and endocrine therapy (if appropriate)

This model is NOT sustainable!
Issues with the Current Survivor Care Model

• Care is **fragmented** and **duplicated**, leading to a poor patient experience and unnecessary cost

Other Care Teams
• Plastics
• Lymphedema/PT
• Medical Genetics
• Fertility
• Women’s Health
• Integrative Medicine

Conclusions

• Up to 1/3 of patients with ER+/HER2-, node-negative breast cancer do not derive benefit from chemotherapy
  • They can be identified by Oncotype DX® evaluation

• For HER2+ breast cancer, dual HER2-directed therapy (Herceptin and Perjeta) combined with chemotherapy can nearly double the pCR rate compared to Herceptin-chemo alone
  • Impact on relapse risk and survival rate are yet to be defined.

• For ER-/HER2- breast cancer, the addition of Carboplatin to standard AC-Taxol increases pCR rates; however, results are mixed as to whether it reduces risk of relapse and improves survival
Conclusions

- For postmenopausal ER+ breast cancer, as compared to 5 years of an aromatase inhibitor, 10 years reduces the risk of a breast cancer event by 34% though absolute gains may be small
  - Nearly as many new breast cancers in the opposite breast were prevented as were relapses in the same breast or elsewhere in the body

- The current model of cancer survivor care is unsustainable and we need to start the conversation and work together for creative solutions to transform the model