CURRENT STATE OF MEDICAL ONCOLOGY
SECOND ANNUAL
BREAST CANCER SYMPOSIUM
October 11, 2014
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OUTLINE
PAST → PRESENT → FUTURE
- BRIEF HISTORICAL REVIEW
- HORMONE RECEPTOR (HR+)
- HER2 DISEASE (HER2+)
- TRIPLE NEGATIVE (TNBC)
- GENETICS

BREAST CANCER INCIDENCE
AND MORTALITY
BREAST CANCER SUBTYPES

SUBTYPES
Luminal A
Luminal B
Her2
Normal
Basal like

*Nature Medicine*
15, 842-844 (2009)
BREAST CANCER CLASSIFICATION

PATHOLOGICAL VARIABLES AND MOLECULAR SUBTYPES CONCORDANCE ~75%

CLINICAL DECISIONS TODAY:
PATHOLOGICAL/CLINICAL VARIABLES...MORE AND MORE MOLECULAR TOOLS

BREAST CANCER THERAPY

ESTROGEN RECEPTOR POSITIVE (ER+)
AND/OR
PROGESTERONE RECEPTOR + (PR+)
BREAST CANCER

MULTIMODALITY THERAPY

Developing 3 strands of therapy

Estrogen Receptor-Negative Breast Cancer

Estrogen receptor-positive breast cancer

Estrogen receptor-negative breast cancer

Cell proliferation
- Controlled by estrogen
- Inhibited by tamoxifen

Estrogen receptor

Tamoxifen inhibits

Estrogen receptor

Cell proliferation
- Not controlled by estrogen
- Not inhibited by tamoxifen
WHAT DO WE KNOW ABOUT ADJUVANT THERAPY FOR HR+ BREAST CANCER?

1) CHEMOTHERAPY: SOMETIMES

1) HORMONAL THERAPY: YES!

Early Breast Cancer Trialists’ Collaborative Group
Lancet 1992;339:71
HORMONE + BREAST CANCER

WHO DOESN’T NEED CHEMOTHERAPY?

PARADIGM SHIFT:

FROM STAGE AND RISK-INFORMED PROCESS TO A TUMOR-BIOLOGY DRIVEN PROCESS

How Well Do Oncologists Estimate Risk and Benefit?

Case:
- 35 year old
- 4 cm tumor, 3+ LN
- ER negative

Loprinzi, et al, JCO 1994

Patient Information

Age: 60

Comorbidity: Major Problems

ER Status: Positive

Tumor Grade: Grade 2

Tumor Size: 1.1 - 2.0 cm

Positive Nodes: 0

Cancer:
- Overview 98 (Taxotere)
- Overview 99 (Like)

Adjuvant Therapy Effectiveness

Hormonal Therapy: 0

Chemotherapy: 0

Combined Therapy: 0

www.adjuvantonline.com

Benefit of chemotherapy in addition to tamoxifen as a function of recurrence score:
Based on NSABP B-30

ONCOTYPE DX - RECURRENCE SCORE

ONCOTYPE DX

 VALIDATION – HR+/LN -

2001: CONSENSUS STATEMENT
2003: ONCOTYPE STARTED TO DEVELOP,
NSABP-14: VALIDATION AS A
PROGNOSTICATOR
2006: NSABP 20: VALIDATION AS PREDICTIVE
2006-2014: STANDARD OF CARE FOR LN-, HR+ EARLY
BREAST CANCER
2013: VALIDATION IN LN POSITIVE DISEASE (1-3 +
LN) ◆ RxPONDER TRIAL
Meta-Analysis of the Decision Impact of the 21-Gene Breast Cancer Recurrence Score in Clinical Practice

Hornberger J, Chien R.
Proc SABCS 2010; Abstract P2-09-06.

META-ANALYSIS / ONCOTYPE DX

Methods

- Meta-analysis performed on seven studies (n = 912)
  - Two retrospective chart reviews
  - One prospective analysis (Lu S et al. J Clin Oncol 2010)
- Studies were included that reported the following:
  - Number of patients who switched from treatment plan of chemotherapy plus hormone therapy (CT+HT) to hormone (HT) only based upon Oncotype DX® Assay Recurrence Score® (RS) (CT+HT -> HT)
  - Number of patients who switched from HT-only treatment plan to CT+HT (HT -> CT+HT) based upon RS

Hornberger J, Chien R. Proc SABCS 2010; Abstract P2-09-06.

Conclusions

- This meta-analysis shows approximately 27-38% reduction in the recommendation of chemotherapy after Oncotype DX assay Recurrence Score testing.
- Overall, the RS changed more than a third of treatment decisions:
  - 33% of the overall population switched from CT+HT to HT only after RS testing.
  - 4% of the overall population switched from HT only to CT+HT after RS testing.

Hornberger J, Chien R. Proc SABCS 2010; Abstract P2-09-06.
WHAT DO WE KNOW ABOUT ADJUVANT THERAPY FOR HR+ BREAST CANCER?

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HORMONAL THERAPY FIRST TARGETED THERAPY META-ANALYSIS

Tamoxifen benefit is all about ER, regardless of other clinical factors

Duration of Tamoxifen: NSABP B-14

NSABP B-14
ER+, LHRH

Placbo
Tamoxifen x 5 yrs

Disease Free at 5 yrs
n=1172

Placbo
n=579
Tamoxifen x 5 years
n=583

Survival

Lancet 2011, 378:773

Adjuvant Endocrine Treatment Options

Menopausal Status at Diagnosis

Initial Therapy
Extended Therapy
Pre / peri-menopausal
Tamoxifen
Tamoxifen

Postmenopausal
Al,
Tamoxifen
Tamoxifen
Al,

What about ovarian suppression? Who does not need 5 years of treatment?

Adapted from ASCO Guidelines 2016. Available at: www.asco.org
BREAST CANCER

HER 2 POSITIVE DISEASE

AGGRESSIVE DISEASE
ONE OF THE MOST TREATABLE / CURABLE

ERB 2 ONCOGENE DRIVER
STANDARDIZATION OF HER 2 TESTING IN PROGRESS

BREAST CANCER – HER 2+

TREATMENT OF MBC
HER2+ - MILESTONE

HER2 and Oncogene Addiction / Driver Mutations: Therapeutic Implications in Breast Cancer

Trastuzumab Added to Chemotherapy Improves OS in HER2+ MBC

Timeline of HER2 Targeted Drug Approval for HER2+ BC

Discovery of erbB2 as an oncogenic driver of breast cancer
Lapatinib approved for 2nd-line Rx of MBC with capecitabine
Herceptin approved for 3rd-line Rx of MBC with paclitaxel and trastuzumab
Trastuzumab approved for 3rd-line Rx of MBC with paclitaxel and trastuzumab
Pertuzumab approved for 3rd-line Rx of HER2+ MBC with trastuzumab and capecitabine
Herceptin approved for 3rd-line Rx of HER2+ MBC with paclitaxel and trastuzumab
Ado-trastuzumab Elovatinib (T-DM1) approved for 3rd-line Rx of HER2+ MBC
HER 2 + BREAST CANCER - ADJUVANT THERAPY

ANTI-HER2 DRUGS

TRASTUZUMAB FOR HER 2 + BREAST CANCER

Monoclonal Antibodies

- Trastuzumab is a humanized monoclonal antibody against EC domain of the HER-2 protein

Mechanism of action:
- Inhibit TK activation
- Induce receptor endocytosis and degradation
- Induce immune-mediated cytotoxicity
HER 2 + BREAST CANCER

Ado Trastuzumab Emtansine (T-DM1)
- Antibody-conjugate
- Binds to HER2 with affinity similar to trastuzumab
- Provides intracellular delivery of mertansine
  - Derivative of maytansine, a natural-product microtubule polymerization inhibitor
  - 20-100 more potent than vinorelbine

ADO TRASTUZUMAB EMTANSINE (TDM-1) – “MAGIC BULLET”

ADO TRASTUZUMAB EMTANSINE (TDM-1)

T-DM1 / ASCO 2012

EMILIA Study Design
- HER2+ (positive) LABC or MBC (trastuzumab)
- Prior taxane and trastuzumab
- Progression on trastuzumab or within 8 weeks of initiation of new therapy
- Stratification factors: World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- Primary end point: PFS by independent review OS, and safety
- Key secondary end point: PFS by investigator; ORR, duration of response, time to symptom progression
PERTUZUMAB

Progression-Free Survival by Independent Review

Overall Survival

CLEOPATRA: Significant improvement in PFS and OS with Pertuzumab
METASTATIC BREAST CANCER – HER2+

HER2+ MBC: An Embarrassment of Riches?

2013-2014 ALGORITHM

Clinical Pathway: HER2 Positive MBC, 2013

1st Line
Taxane + Trastuzumab + Pertuzumab

2nd Line
Ado Trastuzumab Emantansine (T-DM1)

3rd Line and Beyond
Lapatinib + Capecitabine
Trastuzumab + Lapatinib
Trastuzumab + Chemotherapy
*Ado Trastuzumab Emantansine (T-DM1) if not received in 2nd line

MBC HER2+ FUTURE

PHASE III TRIAL: MARIANNE
1st Line HER2+ MBC

Taxane + Trastuzumab

N=1092 HER2+ MBC
First-line

TDM1

TDM1 + Pertuzumab

1st Endpoint: PFS
2nd Endpoints: DFS, TTF, DOB, ORR, CBR

TRIPLE NEGATIVE BREAST CANCER / BASAL LIKE

Breast Cancer Molecular Subtypes

*Unsupervised* gene expression arrays of selected breast cancers

Intrinsic subtypes:
- Differ in biology
- Differ in prognosis
- Differ in treatment response

Basal-like and Claudin-low:
- Usually negative in clinical assays for ER, PR, and HER2
TRIPLE NEGATIVE / BASAL LIKE CONCORDANCE

TRIPLE NEGATIVE BREAST CANCER

Why the Interest in Triple Negative Breast Cancer?
- Only identified subtype with NO targeted therapy
- Poorer prognosis
- Surrogate for molecular subtypes of biologic interest

Approximately 25,000-30,000 cases per year in U.S., but responsible for a disproportionate number of deaths

TRIPLE NEGATIVE BREAST CANCER SURVIVAL

Stage IV Survival Relatively Short

TRIPLE NEGATIVE BREAST CANCER & BRCA MUTATIONS

Summary: Relationship Between BRCA1 and BRCA2 Mutations and Triple Negative Breast Cancer
- Approximately 75% of patients who have a BRCA1 mutation and 10% of patients who have a BRCA2 mutation and in whom breast cancer develops will have the triple negative type.
- Approximately 10–20% of patients who have a BRCA2 mutation and in whom breast cancer develops will have the triple negative type.
- Patients with triple negative breast cancer should consider BRCA testing if they:
  - Have relatives with ovarian or breast cancer
  - Are diagnosed with breast cancer younger than age 50
  - Have suspicious pathology or radiologic test results

SYNTHETIC LETHALITY: BRCA+ & SPORADIC “BRCANESS”

**Synthetic Lethality**

- DNA damage
- PARP deficient
- STOP
- DNA repair

*Graphic courtesy of Harold Burstein, MD, PhD*

METASTATIC TRIPLE NEGATIVE BREAST CANCER

**Summary: Treatment for Metastatic Triple Negative Breast Cancer**

**Standard chemotherapy**

**Treatments under study**

- Platinum therapy
  - Carboplatin
  - Cisplatin
- Poly-ADP ribose polymerase (PARP) inhibitors
  - Olaparib
  - Used as a single agent
  - Benefits patients with BRCA mutations
  - Iniparib (BSI 201)
  - Used in combination with carboplatin/ gemcitabine
  - Benefits patients with triple negative breast cancer (TNBC)

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**Summary: Potential New Targets**

**EGFR**

- Expressed in 90% of triple negative breast cancers
- Single-agent trials with EGFR inhibitor
  - Ererectin (18F)
  - Has been disappointing
- EGFR inhibitor (erlotinib) + cisplatin
  - Improved response rate in patients with triple negative disease

**Phosphatidylinositol-3-kinase (PI3K) kinase**

- Studies are classifying subgroups within triple negative breast cancer on the basis of PI3K mutations
- Potential for identifying subgroups that may be sensitive to PI3K kinase inhibitors

*From:

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**Less promising study results**

- Angiogenesis inhibitors
  - Bevacizumab + paclitaxel
- Tyrosine kinase inhibitors
  - Sorafenib, sunitinib
  - "Dirty" agents (activity on multiple targets)

*From:
BREAST CANCER THERAPY

Weaving together the strands for a unified vision of care

BREAST CANCER ADJUVANT

Adjuvant Treatment for Breast Cancer

ER Negative
- HER2 Negative: Chemo
- HER2 Positive: Chemo & Trastuzumab

ER Positive
- HER2 Negative: Endocrine ± Chemo
- HER2 Positive: Endocrine & Chemo & Trastuzumab

ADJUVANT CHEMOTHERAPY

<table>
<thead>
<tr>
<th>Breast Cancer Subtype</th>
<th>Preferred Adjuvant Chemotherapy Regimen</th>
<th>Preferred Non-anthracycline Regimen</th>
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<tbody>
<tr>
<td>HER2 negative</td>
<td>A/T</td>
<td>TC</td>
</tr>
<tr>
<td>- ER positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- triple-negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AC/T = doxorubicin/cyclophosphamide A/T paclitaxel A/T x 4 FOLFOX 4 x 5 1 x 1
A/C = doxorubicin/cyclophosphamide A/C paclitaxel A/C x 4 FOLFOX 4 x 5 1 x 1
AC = doxorubicin/cyclophosphamide A/C paclitaxel A/C x 4 FOLFOX 4 x 5 1 x 1
CH = capecitabine/oxaliplatin C/H paclitaxel C/H x 4 FOLFOX 4 x 5 1 x 1
T = taxotere
BREAST CANCER GENETICS

Germline mutations in breast cancer

- ATM: 1.4%
- BRCA1: 3.5%
- BRCA2: 2.5%
- BHRP: 2.5%
- CHEK2: 2.5%
- NEK: 2.5%
- PTEN: 2.5%
- RAD51C: 2.5%
- TP53: 2.5%
- None: 95.6%


Genotype/Phenotype Relationships in Hereditary Breast Cancer

<table>
<thead>
<tr>
<th>Genetic Syndrome</th>
<th>Associated Malformations</th>
</tr>
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<tbody>
<tr>
<td>BRCA1</td>
<td>Triple-negative (90%)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>“Normal” distribution</td>
</tr>
<tr>
<td>TP53</td>
<td>HD2B positive (esp. in young men)</td>
</tr>
<tr>
<td>CDH1</td>
<td>Lobular cancers</td>
</tr>
<tr>
<td>PTEN</td>
<td>No specific phenotype</td>
</tr>
</tbody>
</table>

BRCA+ - CANCER RISK

Summary: Risk for Developing Cancer in Women With BRCA1 and 2 Mutations

For BRCA1 mutations
- Lifetime risk for breast cancer: 60%-70%
- Risk begins to increase starting at 30 years of age

For BRCA2 mutations
- Lifetime risk
  - Breast cancer: 40%-50%
  - Ovarian cancer: 10%-12%

TRIPLE NEGATIVE BREAST CANCER RISK

Summary: Special Populations at Risk for Triple Negative Breast Cancer

- African American women are twice as likely to develop triple negative breast cancer than Caucasian American women
- African American women are at highest risk before midlife
- BRCA1/2 and CHEK2 gene testing is strongly recommended for yearly mammograms starting at age 50 or may result in delayed breast and ovarian cancer diagnosis
- Jewish women of Ashkenazi heritage are at a 10 times more likely to have a BRCA1 OR BRCA2 mutation than other women of Western countries
- Women with a personal or family history of triple negative breast cancer or a family history of breast or ovarian cancer should have genetic testing
- A special “Ashkenazi panel” is available to test for BRCA mutations

From

http://cancerstatisticsreview.org/
GUIDELINES FOR BOC GENETIC ASSESSMENT

COMMERCIAL GENETIC PANELS
- AMBRY GENETICS
- QUEST
- LABCORP
- MYRIAD GENETICS
- CLINICAL MOLECULAR GENETICS LAB
- U OF M BIOCHEMICAL GENETICS DX LAB
- NEOGENOMICS LAB
- AMERIPATH

GUIDELINES FOR HBOCS TESTING

CONCLUSIONS

BREAST CANCER: MULTIPLE SUBTYPES. DIFFERENT PROGNOSIS AND THERAPEUTIC IMPLICATIONS

CLINICOPATHOLOGIC CLASSIFICATION THE MOST USED TO MAKE THERAPEUTIC DECISIONS/ ~75% CONCORDANCE WITH MOLEULAR SUBTYPES

CLASSIFICATION FUTURE: MOLEULAR SUBTYPES IS
CONCLUSIONS HR+

PARADIGM SHIFT TO TUMOR-BIOLOGY DRIVEN PROCESS

ADJUVANT CHEMOTHERAPY HAS DECREASED ~30%

OPTIMAL DURATION OF HORMONAL THERAPY 10y?

ROLE OF OVARIAN SUPPRESSION/ABLATION?

OVERCOMING HORMONAL RESISTANCE IS AN EVOLVING AND PROMISING FIELD

CONCLUSIONS

HER 2 +: AGGRESSIVE DISEASE/EFFECTIVE TREATMENT

ADVANCES: TRASTUZUMAB, PERTUZUMAB, TDM-1, LAPATINIB

TNBC: AGGRESSIVE DISEASE, NO SPECIFIC BIOLOGIC TREATMENT, POOR PROGNOSIS

GENETICS: A LOT NEW MUTATIONS, UNCLEAR IMPLICATIONS FOR PATIENTS AND DOCTORS

Thank you!