Understanding and Optimizing Treatment of Triple Negative Breast Cancer

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Objectives

Discuss:

1. Factors associated with breast cancer cell growth and metastases.
2. Molecular profile associated with triple negative breast cancer.
3. Epidemiology and clinical characteristics of triple negative breast cancer.
4. Therapeutic options and future research endeavors.
Cancer Growth and Metastases

A tumor grows from a single cancer cell.

Cancer cells invade neighboring tissue.

Cancer cells spread through lymph and blood vessels to other parts of the body.
Angiogenesis is one of the fundamental hallmarks of cancer.

- Self-sufficiency in growth signals
- Insensitivity to antigrowth signals
- Tissue invasion and metastasis
- Limitless replicative potential
- Sustained angiogenesis
- Evading apoptosis

Adapted from Hanahan and Weinberg. *Cell.* 2000;100:57.
Targeted Therapies

Growth factor
Estrogen

Plasma membrane

ER

Cytoplasm

PI3-K

AKT

mTOR

p90RSK

MEK

MAPK

Nucleus

Basal transcription machinery

ERE

ER Target gene transcription

CCR New Strategies
Breast Cancer Management

• Breast cancer is not all the same
• Types of breast cancer
  - Invasive ductal vs invasive lobular vs others
• Subtypes of invasive ductal carcinoma
  - Classification by receptor studies/IHC markers
  - Classification by gene expression profiles
Types of Breast Cancer

- ER/PR +, Her-2/neu +
- ER/PR +, Her-2/neu -
- ER/PR -, Her-2/neu +
- ER/PR -, Her-2/neu -
Why is subtype important?

- Different outcomes
- Prognostic significance
- Selection of therapeutic options
- Response to treatment
Molecular Phenotypes
Molecular Portrait of Breast Cancers

"Intrinsic" gene set on 78 single tumor samples

5 “clusters”
- Basal-like
- HER-2
- “Normal”
- Luminal B
- Luminal A

476 cDNA clones

85 Arrays

Gene Expression Patterns of Breast Carcinomas Predict Survival

Adapted from Sorlie et al. PNAS, 2001
What’s in a Name? Clinical Phenotype vs Molecular Subtype

Triple negative but not basal 10%-30%
Can also include “claudin-low,” a subtype notable for high expression of stem cell markers

Basal but not triple negative
15%-40% are ER+, PR+, or HER-2+

When we talk about “triple-negative” breast cancer, we are mostly (but not entirely) talking about the basal-like molecular subtype.
Who gets triple negative breast cancer?

• 15% of breast cancer in US
• Young women
• African American women
• BRCA1 positive

• Any woman can get any type of breast cancer
“Basal-Like” breast cancer

- Based on which genes are upregulated and downregulated in a cancer
- 70-90% of triple negative cancers are basal-like
- Resemble basal cells that line the milk ducts
- Have defective gene repair and genomic instability
Triple-Negative Disease
ER-, PR-, and HER2 Negative

• Unique characteristics
  – Comprises about 15% of all breast cancers
    • 39% young African American women
  – Linked to BRCA1 mutation carriers
  – High grade and highly proliferative
    • Poor prognosis
  – High risk of early distant relapse

Can Morphologic Criteria Enhance Screening for BRCA1 Mutations?

- 7% of breast cancer cases & 10% of ovarian cancer cases associated with an autosomal dominant pattern of inheritance
- Approximately 80% of BRCA1 associated tumors have triple negative (ER-/PR-/Her-2) phenotype.
- High rate of BRCA1 mutations in young women with breast cancer who have both ER negative and poorly differentiated tumors

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- Should all breast cancer patients with a triple negative phenotype be screened for BRCA1 mutations?
- Would this improve the rate of detection over using personal hx, family hx, and ethnicity for screening?
Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients; a single-institution compilation compared with the National Cancer Institute SEER database (Morris, Mitchell et al).

- **Results**: More AA pts presented with advanced stage (AS) tumors in both databases, and higher histologic grade (p<0.001) and nuclear grade than C pts (p<0.001).
- AA pts had lower ER-positivity (51.9% vs. 63.1%, p<0.001) but significantly higher ki-67 (42.4% vs. 28.7%, p<0.001) and p53 expression (19.4% vs. 13.1%, p<0.05) than C pts with all stages of tumors.
- Basal or “triple-negative” breast cancer phenotype was found to be more common in AA pts as compared with C pts (20.8% vs 10.4%, p<0.0001), associated with higher histologic and nuclear grade (p<0.0001).
Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients; a single-institution compilation compared with the National Cancer Institute SEER database.

- **Conclusions:** AA pts with invasive breast carcinomas are more likely to present with later stage, higher grade, higher ki-67 expression, and less likely to have ER positivity than C pts in both the NCI SEER and TJUH databases. Due to these disparate presentations, molecular studies which may explain these differences, and correlations with survival, are proposed.
Chemotherapy kills growing cells

Targeted Therapies

Herceptin, Lapatinib

Tamoxifen, Arimidex, Faslodex, Aromasin, Femara

Growth factor
Estrogen

IGFR

PI3-K

AKT

mTOR

p90Rsk

MAPK

SOS

RAS

RAF

MEK

Nucleus

Basal transcription machinery

ERE

ER Target gene transcription

Cytoplasm

PI3-K

Cell survival

Cell growth

Plasma membrane

CCR New Strategies
Triple Negative Breast Cancer Treatment

- Chemotherapy
- Parp inhibitors
- EGFR inhibitors
- Angiogenesis inhibitors
- Tyrosine Kinase inhibitors
- One trial in metastatic TNBC patients.
- Gemcitabine/carboplatin
- Improvement in tumor response and survival with Parp inhibitors.
EGFR inhibitors

- Two trials in metastatic breast cancer
  - Irinotecan/carboplatin + cetuximab
  - Cetuximab alone or with carboplatin
Angiogenesis

- Taxol + Avastin in metastatic patients
- Benefit in triple negative patients
Tyrosine Kinase Inhibitors

- Early trials of multiple agents in metastatic TNBC

Diagram showing an example of how growth inhibitors can block more than one action in a cell (multi TKI).

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Myths about triple negative breast cancer

- There are no effective treatments.
- Patients are doomed to relapse.
- Women with triple negative cancers are doomed to die of their disease.
- You have to have a mastectomy for triple negative breast cancer.
Effectiveness of Chemotherapy
Triple Negative / Basal Disease
Basal-like Breast Cancer and Neoadjuvant Chemotherapy

Gene expression array subtyping and pathologic complete response to T-FAC neoadjuvant chemotherapy

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<td>HER2</td>
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<td>Luminal</td>
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P < 0.001

Rouzier R et al, SABCS 2004
**Basal-like Breast Cancer and Neoadjuvant Chemotherapy (UNC)**

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<td>Clinical CR</td>
<td>Clinical PR</td>
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<td>32 %*</td>
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**Pathologic stage post-chemotherapy**

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<tr>
<td>HER2+</td>
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<td>14 %</td>
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<tr>
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* *p < 0.05

Carey LA, SABCS 04
Rates of distant recurrences in triple-negative and other breast cancers

Rates of breast-specific survival in triple-negative and other breast cancers.
Rates of distant recurrences following surgery in triple-negative and other breast cancers.


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Triple Negative Breast Cancer

- Represents a subtype of breast cancer with unique molecular and clinical characteristics.
- Characterized by more aggressive clinicopathologic features including younger age, higher mean tumor size, and higher-grade tumors.
- More likely to occur among premenopausal women of African-American descent.
- Association with BRCA1 mutation status.
- More likely to develop a recurrence during the first 3 years following therapy.
- More aggressive visceral and soft-tissue relapse and less common bone recurrence.
- High response to systemic chemotherapy.
Future Directions

• Increase participation in clinical trials.
• Design and implement cancer prevention trials applicable to at risk populations.
• Increase understanding of risk factors and biology underlying triple-negative breast cancer.
• Improving treatment strategies.
• Continuous review of current methods.
Mission

To develop comprehensive programs to facilitate research, education, training and teaching, access to quality supportive services including palliative and survivorship care, and workforce diversity initiatives that will reduce and lead to elimination of cancer healthcare disparities in the KCC population.
Resources to Enhance Diversity and Assist Minority Populations

Breast Cancer Video
“African-American Women CAN Beat Breast Cancer”
- Developed in partnership with Region II of the NMA and the Eastern Cooperative Oncology Group.
- Recipient of the
  - 2001 Aegis Award for outstanding video production
  - 2001 Bronze Telly, one of the most sought after awards in the television and video industries.

“The Colon Cancer Puzzle: Putting all the right pieces together to beat it”
- Received Bronze Telly in the category of Health and Wellness.

“Guía de Ensayos Clínicos para Pacientes con Cáncer”
Questions?

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