BREAST CANCER: NEW ADVANCES AND TREATMENT PARADIGM

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OBJECTIVES

1. Recognize the high risk patient
2. Review key advances in breast cancer therapy
BREAST CANCER

1 in 8 women are diagnosed with breast cancer

Approximately 250,000 new cases/year are diagnosed in the US

Only 5-7% are hereditary

Main risk factors: age, female
WHO IS THE HIGH RISK PATIENT?

- Known genetic mutation
- Family history of cancers that are part of a syndrome
- Lifetime risk of 20-25% using risk calculators based on family history
- High risk breast lesions
  - Atypical ductal hyperplasia
  - LCIS
HISTORY

A 30 year old lady with no significant past medical history came to clinic today for routine followup.

**Family history** is significant for malignancies on her maternal side:

- Breast: mother (49), aunt (52)
- Ovarian cancer: grandmother (59)
NEXT STEPS

Refer to Genetics Clinic

Results: Negative for deleterious mutations in 20 genes

**Question:** Is this patient still a high risk patient?
RISK CALCULATORS

Tyrer-Cuzick model
Gail model
ID:
Age is 30-yrs.
Age at menarche unknown.
No information about childbirth.
Premenopausal.
Height is 5 ft 5 in.
Weighs 8 st 130 lb (or 242 lb).
Never used HRT.

Competing mortality projection
Risk after 10 years is 1.6%.
10 year population risk is 0.5%.
Lifetime risk is 26.1%.
Lifetime population risk is 11.2%.
Probability of a BRCA1 gene is 1.54%.
Probability of a BRCA2 gene is 2.86%.
HIGH RISK LESIONS

Atypical Ductal Hyperplasia: 25-30% lifetime risk

LCIS: 25-30% lifetime risk
HIGH RISK SCREENING

Annual mammogram
Annual breast MRI
Clinical breast exam every 6 months
GENETIC SYNDROMES
(BRCA, CHEK2, PALB2 ETC)

Consider prophylactic surgeries
BREAST CANCER TREATMENT PARADIGMS
HISTORICALLY:

STAGE: most important determinant of treatment

- Size
- Lymph node status
- Presence of distant metastasis

TNM Staging
CASE

1.9 cm tumor
No lymph node involvement
No symptoms suggestive of distant metastasis

Stage IA  T1c N0 M0
Good?
BREAST CANCER IS NOT ONE DISEASE BUT MANY

- Tumor biology is the most important determinant of distant recurrence
ONE IS NOT LIKE THE OTHER........
MORE LIKE THIS.........
CLINICOPATHOLOGIC CRITERIA

- Important but imperfect predictors of recurrence
3 MAJOR TUMOR SUBTYPES

Depends on presence or absence of molecular markers for:

- Estrogen receptors (ER)
- Progesterone receptors (PR)
- Her2 neu
**HR +/ Her2 negative (70%)**

**HER2 positive (15-20%)**

**HR- /Her2 - (15%)**
MOLECULAR TARGETS IN BREAST CANCER PATHOGENESIS

ESTROGEN RECEPTOR ALPHA

• Steroid hormone receptor
• Transcription factor

**Therapy:** Endocrine agents that target estrogen signaling pathway

ERBB2 (Her2/neu)

A transmembrane tyrosine receptor kinase in the epidermal growth factor family and is overexpressed in 20% of breast cancer

**Therapy:** anti ERBB2 antibodies or small molecule tyrosine kinase inhibitor
STAGE 1A  T1c N0 M0 (ER+/ PR+/ HER2 -)

1.9 cm tumor
No lymph node involvement
No symptoms suggestive of distant metastasis
Stage 1A  T1c N0 M0 , ER+/PR+, Her2-
Good?
TOOLS THAT CAN ESTIMATE RISK OF 
RECURRENCE
GENE EXPRESSION PROFILING

Recurrence Score (Oncotype Dx testing)

21 genes

- Prognostic
- Predictive
**Figure 1 | Oncotype DX Recurrence Score (RS) Genes and Algorithm**


Note: ER - Estrogen receptor; PR – Progesterone Receptor
OncoType DX Breast Recurrence Score® Report

Node Negative

Recurrence Score®
Result (RS) 10

Distant Recurrence Risk at 9 Years
With AI or TAM Alone
TALOVA
10% Recurrence Likelihood / TAM - Terazolom

Absolute
Chemotherapy Benefit
<1%

*Exploratory Subgroup Analysis for TAILORx and NSABP B-20:
Absolute Chemotherapy (CT) Benefit by Age and RS

<table>
<thead>
<tr>
<th>Age</th>
<th>RS 0-10</th>
<th>RS 11-25</th>
<th>RS 26-25</th>
<th>RS 26-100</th>
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<td>&gt;50 years</td>
<td>No CT Benefit (&lt;1%)</td>
<td>&gt;15% CT Benefit</td>
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Quantitative Single-Gene Scores

11.4 ER Positive
8.3 PR Positive
9.0 HER2 Negative
Oncotype DX Breast Recurrence Score® Report
Node Negative

PATIENT, SAMPLE
Date of Birth: 01-Jan-1950  Gender: Female  Report Number: OR000123456-3260  Report Date: 14-Jan-2019
Specimen Source ID: Breast/SP.16_0123456  Ordering Physician: Dr. First/Last Name

Recurrence Score® (RS) Result

32

Distant Recurrence Risk at 9 Years

With AI or TAM Alone

20%
95% CI (15%, 27%)
NSABP B-18

Group Average Absolute Chemotherapy (CT) Benefit* RS 26-100 All Ages

>15%
95% CI (9%, 37%)
NSABP B-20

Exploratory Subgroup Analysis for TAILORx and NSABP B-20: Absolute CT Benefit for Distinct Recurrence by Age and RS Result

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<td>~6.5% CT Benefit</td>
<td>&gt;15% CT Benefit</td>
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Quantitative Single-Gene Scores

10.2 ER Positive

-0.7 0.8

6.4 PR Positive

-2.2 6.1

8.4 HER2 Negative

-2.1 12.1
EXAMPLES OF OTHER ASSAYS

• The **Breast Cancer Index test** is used to predict the risk of node-negative, hormone-receptor-positive breast cancer coming back 5 to 10 years after diagnosis.

• The **MammaPrint test** is used to predict the risk of recurrence within 10 years after diagnosis of stage I or stage II breast cancer that is hormone-receptor-positive or hormone-receptor-negative.
STAGE 1A  T1C N0 M0 (ER-/ PR-/ HER2 +)

1.9 cm tumor
No lymph node involvement
No symptoms suggestive of distant metastasis

Stage 1A  T1c N0 M0 , ER-/PR-, Her2+
Good?
TREATMENT

- Her2 targeted agents (trastuzumab +/- pertuzumab)
- Chemotherapy

Add endocrine therapy if ER+
EXAMPLES OF HER2 TARGETED COMBINATION REGIMENS

Weekly paclitaxel x 12 + Trastuzumab X 1 year

Taxotere/Carboplatin/Trastuzumab/Pertuzumab Q3 weeks x 6 → trastuzumab or Kadcyla
STAGE 1A  T1c N0 M0 (ER-/ PR-/ HER2 -)

1.9 cm tumor
No lymph node involvement
No symptoms suggestive of distant metastasis

Stage 1A  T1c N0 M0 , ER-/PR-, Her2-

Good or Bad?

TRIPLE NEGATIVE BREAST CANCER
TRIPLE NEGATIVE BREAST CANCER

Unfavorable prognosis

Chemotherapy considered in tumors >5mm.

Response to Neoadjuvant therapy: Prognostic

Biologically aggressive, specially the 1st 3 years
TREATMENT

LOCAL THERAPY
- Surgery
- Radiation

SYSTEMIC
- Chemotherapy
- Endocrine therapy
- Her2 targeted agents
LOCAL THERAPY

< 5 cm tumor, no lymph node involvement
   Lumpectomy + Radiation
or Mastectomy

> 5 cm tumor or with lymph node involvement
   Lumpectomy + Radiation
   Mastectomy + Radiation
90% are Early Stage at Presentation
10% are metastatic

GOAL OF THERAPY:
Early stage- CURE. Eradication of Micrometastatic disease
Metastatic- PALLIATIVE
EARLY STAGE DISEASE

**SYSTEMIC THERAPY** is determined by hormone receptor/Her2 neu status

**ER +:** Endocrine therapy

Some need chemotherapy. Now there are tools (molecular and clinical) for prognostication

**Her2 +:** Add Her2 targeted agents with chemotherapy

**Triple negative:** Chemotherapy
TIMING SYSTEMIC THERAPY

Neoadjuvant versus Adjuvant
RATIONALE FOR NEOADJUVANT THERAPY

- Downsizing tumor for breast conservation or to improve chance of margin clearance
- Prognostication
Prognostic impact of pathologic complete response (pCR) on disease-free survival (DFS) in 4,193 patients according to breast cancer intrinsic subtype. (A) Patients with luminal A-like tumors, (B) luminal B/human epidermal growth factor receptor 2 (HER2)-negative-like tumors, (C) luminal B/HER2-positive-like tumors, (D) HER2-positive (nonluminal)-like tumors, and (E) triple-negative tumors; (F) comparison of DFS in 717 patients achieving pCR according to breast cancer intrinsic subtype.

JCO 2012, 30, 1796-1804 Gunter von Minckwitz; Michael Untch; Jens-Uwe Blohmer; Serban D. Costa; Holger Eidtmann; Peter A. Fasching; Bernd Gerber; Wolfgang Eiermann; Jörn Hilfrich; Jens Huober; Christian Jackisch; Manfred Kaufmann; Gottfried E. Konecny; Carsten Denkert; Valentina Nekljudova; Keyur Mehta; Sibylle Loibl;
NEOADJUVANT THERAPY: TYPICAL PATIENTS

1. Triple negative (ER-/PR-/Her2-)
2. Her2 + disease
3. Locally advanced/ lymph node positive
4. Frail patients with ER+ disease
COMMON AGENTS
TAMOXIFEN

Advantages

- EFFICACY
  Established in breast cancer treatment/prevention

- BENEFITS
  Bone and lipid/CVD benefits

Disadvantages

- EFFICACY
  Limited to ER/PR + disease

- TOXICITIES
  - Endometrial cancer
  - Blood clots
  - Hot flashes
  - Vaginal/urinary symptoms
Aromatase inhibitors block this conversion

Lowers the levels of estrogen by >95% in postmenopausal women

AIs are not effective in women with intact ovarian function
SIDE EFFECTS OF AROMATASE INHIBITORS

- Hot Flashes
- Vaginal Dryness/Atrophy
- Mood changes
- Myalgias/Arthralgias
- Osteopenia/Osteoporosis
- Lipid
CHEMOTHERAPY SIDE EFFECTS

- Myelosuppression
- Peripheral Neuropathy
- Alopecia
- Nausea/Vomiting
- Diarrhea
- Mouth Sores
PARP INHIBITORS
BRCA

Tumor suppressor genes that function in DNA repair

The only DNA alterations with an associated targeted therapy

Inhibition of PARP enzymes have been shown to specifically target BRCA deficient cells by synthetic lethality

FDA approved: olaparib and talazoparib
Homologous recombination (HR) DNA repair seeks to repair double strand breaks to avoid the genetic turmoil that leads to cancer.

However, the presence of BRCA mutations interferes with this process, and can instead cause errors in DNA repair that give rise to cancer.

An alternate method of repair of single broken strands of DNA, is via PARP.

Blocking the protein PARP, can cause double strand breaks to form, killing BRCA cancer cells selectively.
PARP INHIBITORS IN BRCA PATIENTS
CDK4/6 INHIBITORS
CDK 4/6

The cyclin D1-CDK4/6-Rb axis appears to be most active in ER+ breast cancers.

The \textit{CCND1} gene encoding cyclin D1 is amplified in 15% to 20% of all breast cancers → cyclin D1 protein is overexpressed in more than 50% of cases.

Cyclin D1 gene amplification occurs most commonly in ER+ luminal B.
CDK 4/6

Cyclin dependent kinase (1-6) coordinate cell cycle progression, CDK 7-9 downstream effects as transcriptional regulators.

Cyclins act as a regulatory subunit to control kinase → allowing progression of cell cycle (G1 to M).

CDK 4, CDK 6 and CKD2 → phosphorylate retinoblastoma protein (Rb).

Rb acts as tumor suppression (blocks S phase progression). Rb is inactivated by phosphorylation.

3) Mechanisms of therapeutic CDK4/6 inhibition in breast cancer. Susan Combs Scott, Srah S. Lee and Jame Abraham. Seminars in Oncology, 2017-12-01, Volume 44, Issue 6, Pages 385-394,
CDK 4/6 INHIBITORS
SUMMARY

Recognize the high risk patient

- History is important
- Risk calculators
- High risk screening +/- chemoprevention

Review key advances in breast cancer therapy

- Subtypes
- Tools to calculate recurrence
- New drugs
THANK YOU