Prognostic and Predictive Assays for Personalizing Breast Cancer Therapy

Outline

- Ki67
- Prognostic and Predictive markers
- Predictors of therapy toxicity
Major concerns...

- Histological grade
  - Poor reproducibility (NSABP B14)
  - Overall concordance 43%
    - 61: 36%
    - 62: 23%
    - 63: 61%
- Ki67
  - Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group
  - Paik et al, N Engl J Med 2004
  - Dowsett et al, J Natl Inst 2011

An international Ki67 reproducibility study

Inter-observer consistency was good:
- 6 labs scored same 50 cases 3 times
- Overall ICC = 0.94 (0.92, 0.97)
- Formal counting methods yielded more consistent results over visual estimates.

Intra-observer variability was evident
- 6 labs scored same 50 cases 3 times
- Overall ICC = 0.94 (0.92, 0.97)
- Formal counting methods yielded more consistent results over visual estimates.

Training may improve consistency

Evaluation of an optimal cut-off point for the Ki-67 index as a prognostic factor in primary breast cancer

Immediate fixation
- 18 hrs to fixation

Suitable fixation
- Poor fixation
Development of a Highly Reproducible Clinical Test for Ki67 Using AQUA® Technology

Accuracy of ki67 scoring using AQUA® technology

Decreased variability in ki67 scoring by AQUA® technology

Concordance CNB vs surgical specimen

- 225 cases
- Concordance 76.9%
- Lower than ER (95.6%), PgR (88.0%), and HER2 (91.5%), p<0.001
- Review by automated analyzer 96.3%

Ki67 levels in pretherapeutic core biopsies as predictive and prognostic parameters in the neoadjuvant GeparTrio trial

≤15% vs. 15.1–35% vs. >35%

pCR rate (%)
disease-free survival rate
overall survival rate

Mizuno et al. SABCS 2012

Dankert et al. SABCS 2012
Strong prognostic concordance between Ki67 and binary but not multi-level gene expression signatures

Tobin et al. SABCS 2012

Take home messages

- Immunohistochemistry for Ki67 is currently not reliable for precise measurement of the proliferating fraction of breast cancer
  - Could improve with a standardized interpretation method
  - Other technical and pre-analytical factors pose a challenge
  - New technologies being used
- Proliferation is generally associated with likelihood of pathologic complete response from chemotherapy
- Predicted response is paradoxically associated with worse survival

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Predictive Genomic Markers to Chemotherapy and Adjuvant Trastuzumab via Whole Genome Expression DASL Profiling in the N9831 Adjuvant Study

N9831 Adjuvant Study

32 genes correlated with outcome, p<0.001

Major functional categories
- Receptor signaling (7 genes)
- Chromatin/transcription (6 genes)
- Cell death (4 genes)
- Cell cycle (3 genes)
- Wnt signaling (3 genes)
- Lipid signaling (3 genes)

PIK3CA mutations are linked to PgR expression: A Tamoxifen Exemestane Adjuvant Multinational (TEAM) pathology study

PIK3CA mutations are present in 40% of luminal breast cancers
PIK3CA is not an independent risk factor in ER+ disease

Biomarker analysis in CLEOPATRA: a phase III, placebo controlled study of pertuzumab in HER2 positive, first-line metastatic breast cancer

PIK3CA mutation associated with poorer prognosis (both arms)
Vitamin D, But Not Bone Turnover Markers, Predict Relapse In Women With Early Breast Cancer: An AZURE Translational Study

**Insufficient Baseline 25OH-Vitamin D Predicts Recurrence**

- Mean (SD) vitamin D: 18.2 (9.25) ng/ml – Range: <3-54.82 ng/ml

Association Between the 21-Gene Recurrence Score (RS) and Benefit from Addition of Adjuvant Paclitaxel in Node-positive, ER-positive Breast Cancer Patients: Results from NSABP B-28

**Benefit of Adding Paclitaxel to AC**

- **Background**
  - GGI reclassifies some intermediate grade tumors into high or low risk
- **Methods**
  - GGI & central Ki67 assessed in BIG 1-98 patients treated with letrozole or tam (N=1183)
  - Ki67 > 14% defined as high (per St. Gallen)
  - GGI and Ki67 capture similar information (proliferation)
  - But, GGI didn’t reclassify about 40% of tumors into low or high risk

Independent validation of genomic grade index (GGI) in BIG 1-98

- **Background**
  - GGI reclassifies some intermediate grade tumors into high or low risk
- **Methods**
  - GGI and Ki67 assessed in BIG 1-98 patients treated with letrozole or tam (N=1183)
  - Ki67 > 14% defined as high (per St. Gallen)
EndoPredict Score identifies late distant metastasis in ER+/HER2- breast cancer patients

Dubsky et al. SABCS 2012

Metabolic Syndrome and Recurrence within the 21-Gene Recurrence Score Assay Risk Categories in Lymph Node Negative Breast Cancer

- To investigate whether or not MS would predict BC recurrence as defined by the risk categories of the RS
- 332 patients with newly diagnosed ER+, node- disease
- Standard systemic and local therapy
- WHO definition for MS (at least 2 of the following: HTN, dyslipidemia, central obesity, and microalbuminemia)

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<tr>
<th>Odds Ratio of Recurrence by OncoDX Group</th>
<th>.95 CI, Odds Ratio</th>
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<tr>
<td>Low score (0-17)</td>
<td>MetS Yes vs No</td>
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<td>Intermediate score (18-22)</td>
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<td>High score (23-100)</td>
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Lakhani et al. SABCS 2012

Molecular characterization of residual TNBC after NCT

Balko et al. SABCS 2012
Clinically targetable pathways in TNBC

All together these data show that TNBC after adjuvant chemotherapy is heterogeneous and has multiple alterations that are targetable with existing drugs in development.

Take home messages
- Genomic signature can predict for trastuzumab benefit in arm C of N9831
- The role of PIK3CA mutations still under study in ER+ breast cancer
- PIK3CA mutations correlated with worse outcome in patients receiving anti-HER2 therapies
- The RS did not significantly predict benefit from the addition of paclitaxel to AC in B-28
- EndoPredict may help select patients for extended therapy, but requires validation
- GGI and Ki67 capture similar information (proliferation)
- Keep Vitamin D levels in a good range if you use bisphosphonates
- MS is an independent risk factor for BC recurrence among low risk women with LN negative, ER positive BC treated with standard adjuvant therapy
- TNBC after adjuvant chemotherapy is heterogeneous and has multiple alterations that are targetable with existing drugs in development

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**Take home messages**

- Pharmacogenomics may help us to identify patients at risk for toxicity
- Routine screening of metastatic breast cancer patients for DRB1*07:01/DQA1*02:01 allele carriage is not recommended prior lapatinib therapy
- CYP2C8*3 increases risk of paclitaxel-induced peripheral neuropathy, with an approximate doubling of neuropathy risk for each *3 variant a patient carries
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Thank you !!!!

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