Neoadjuvant Strategies in DCIS

Henry Mark Kuerer, MD, PhD, FACS

Department of Surgical Oncology
MD Anderson Cancer Center
Preoperative Therapy Invasive Breast Cancer
Why not utilize for DCIS? Potential Advantages?

- ‘Tumor’ Downsizing
  - Mastectomy → BCT
- *In vivo* assessment of response
- Molecular determinants of response:
  - May expedite new and better drug development

Esserman *et al* Ann Surg Onc 2004
Breast Cancer Develops Over Time

• Breast cancer cells progress through changes over a period of years

Normal Duct

Ductal Hyperplasia

Ductal Hyperplasia with Atypia

Ductal Carcinoma In situ

Invasive Ductal Carcinoma

Reversible with Tamoxifen

Reversible?
UCSF Preoperative Endocrine Treatment for ER-positive DCIS

N= 62

3-month

- Letrozole 2.5 mg PO QD
- Tamoxifen 20 mg PO QD

Exclusion criteria:
- palpable disease
- microinvasion
- not visible on MRI

Chen et al, *BMC Cancer*, 2009
Alteration of biomarker expression is associated with endocrine treatment for DCIS

Chen et al, *BMC Cancer*, 2009
Biomarker changes associated with endocrine treatment

Ki67, premenopausal

Ki67, postmenopausal

CD68, premenopausal

CD68, postmenopausal

Chen et al, BMC Cancer, 2009
MRI assessment of letrozole response

Responder: ER-positive, postmenopausal
MRI assessment of letrozole response

Responder: ER-positive, postmenopausal; “pathologic CR"
Three-Month Pre-op Endocrine Therapy in DCIS

• Preoperative endocrine therapy of ER-positive DCIS
  – Safe
  – Histologic and radiologic changes are evident

• No long term data on efficacy and the question remains in what proportion of women might this therapy actually prevent the occurrence of invasive breast cancer
NEW Trial Alliance-CALGB 40903: Phase II Single-Arm Study of Neoadjuvant letrozole for ER(+) postmenopausal DCIS

- Registration
- MRI Core bx
- Clinical exam
- MMG
- MRI
- Surgery

3 months Letrozole

stable or responding

progression

3 months Letrozole

MMG MRI

Measure change Ki67, Imaging-path correlation
PI: Shelley Hwang
N=96

3/1/14: 43
LORIS Trial in UK 2014
Watch and Wait: Active Surveillance

- Screen detected low/intermediate grade DCIS, > 46 years
- Randomize surgery versus no surgery
  - Non-inferiority trial 932 patients
  - Primary endpoint: 5 year invasive disease at 5 year
  - Secondary: Mastectomy rate, quality of life, biomarkers
Trastuzumab for DCIS?

Kuerer et al. *CANCER*, 2011
HER-2/Neu Gene Amplification in DCIS

- High grade - 56%
- Low grade - 19%
- This also parallels IDC with DCIS

Hoque et al, *Cancer Epi & Prev* 2002
Can we selectively eradicate or prevent HER-2 + invasive breast cancer?

ER Neg HER2 + DCIS

Trastuzumab

ER Neg HER2 + Invasive
MDACC Preoperative Trastuzumab Schema for DCIS

DCIS by Core Biopsy Her 2+

Trastuzumab 8 mg/kg X One-dose

SURGERY at 3 weeks Segmental or Mastectomy

- Ki67
- cCaspase-3
- Pathologic & Immune Response

CONSENT

- Blood
- Ki67
- cCaspase-3
Trastuzumab for DCIS Trial
Clinical Pathologic Factors

• Median age: 53 yrs
• Mean Mammographic Size: 5.1 cm
• Overall ER+: 80%
• Overall HER2+: 35%
• Total eligible: 24 patients HER2 Pos
  – 12 patient samples not receiving drug used as control experiments
Immune Response Studies

• Patient’s PBMC and Serum obtained
  – Before and after Trastuzumab therapy
  – Evaluated for ADCC
  – Development of HER2 Specific CD4 response
  – Laboratory of Radvanyi/Vence MDACC

Proliferation and Apoptotic Markers

\textit{Ki67 and Cleaved Caspace-3}
Change in Proliferation: Ki-67

Mean Pre-therapy Ki-67 Staining = 44.3 +/- 3.4 %
Change in Apoptosis: CC3

Mean Pre-therapy CC3 Staining= 2.6 +/- .8 %
Histopathologic Changes

• NONE seen
Antibody Dependent Cellular Cytotoxicity

Target cells = HER2 overexpressing MDA-MB361
Patient’s NK Cells Actively Kill HER2 Target Cells

- Patient’s CD56+ NK cells are functional in presence of HER2+ target cells and trastuzumab
- CD107a+ = degranulating NK cells

\( P = 0.00012 \)

![](image-url)
Trastuzumab for DCIS

• Trastuzumab can induce specific immunity in pts w HER2+ DCIS after 3 weeks of treatment

• Future studies-
  – PRE-surgical
  – What kind of histologic response should we be looking for?
  – Which biomarkers to measure?
Adding Pertuzumab to Trastuzumab in Invasive Breast Cancer NeoSphere Trial pCR Rates

*Pathologic complete response (pCR) rate defined as the absence of invasive cancer in the breast at the time of surgery. T = docetaxel; H = trastuzumab, P = pertuzumab.

Preoperative Vaccines for DCIS?
Targeting HER2 with Dendritic Cells

Brian J Czerniecki, MD, PhD, FACS
University of Pennsylvania

Protocol for DC Preparation

**LEUKAPHERESIS**

**Input** Mononuclear Cells

**Outflow** Elutriation Fractions

**ELUTRIATION**

**Monocytes**

**SFM**

**VACCINATION**

DC1 Activated with GM-CSF, IL-4, IFN-γ, LPS, pulsed with MHC class II and MHC class I **HER-2/neu peptides**, 40 hours total culture.
HER-2/neu Pulsed DCs for Treatment of DCIS

- Neoadjuvant study; N=38
- 4 weekly nodal vaccinations
- MHC class II and class I HER-2/neu peptides
- Follow-up immune response
- Surgical Therapy

Trafficking of Lymphocytes into Breast Post-vaccination

CD4

Pre

CD8

Post

Pre
Anti-HER-2/neu CD4+ T cell Memory Post-Vaccination

Graphs showing IFN-γ (pg/ml) levels before (pre), after (post), and 2 years post-vaccination for T cell only, P42-56, P776-790, and BRAF groups. The graphs indicate a significant increase in IFN-γ levels post-vaccination compared to pre-vaccination levels, with the BRAF group showing the highest increase. The graph on the right indicates spots/40,000 cells post-sentinel node vaccination.
Prevention of Breast Cancer Using a Dual Tyrosine Kinase Inhibitor

Lapatinib

- Inhibits EGFR and Her2/neu kinase complexes to blockade downstream signal transduction pathways
- FDA approved for the treatment of patients advanced and metastatic breast cancer
- Now being tested for adjuvant treatment of early-stage breast cancer
Model of ER- Breast Cancer: MMTV-erbB2 Transgenic Mice

MMTV-erbB2

P Brown, MD, PhD

ER-negative tumors

Normal Mammary Glands

Hyperplasia

DCIS (MIN)

Invasive Cancer

3-6 months

4-7 months

6-10 months

H & E

IHC for ERα

ER-alpha negative
Prevention of Mammary Tumors by Lapatinib

Randomize

Endpoints:
- Time to Tumor Formation
- Tumor Number
- Biomarker Expression

MMTV-erbB2 Mice

Treat twice daily by oral gavage

3 mos

16 mos

Lapatinib (75 mg/kg) N = 20
Lapatinib (30 mg/kg) N = 20
Vehicle N = 20

Survival

Days on Treatment

P < 0.001

0.0 0.2 0.4 0.6 0.8 1.0

Lapatinib (75mg/kg)
Lapatinib (30mg/kg)
Vehicle

70%

Brown et al
JNCI, 2009
LAPIS Trial (LAPatinib for In Situ Breast Cancer)

**PI:** Powel Brown

**Endpoints**

**Primary:**
1. Proliferation (Ki67 IHC) in DCIS
2. Toxicity

**Secondary:**
1. DCIS Incidence on excision
2. Modulation of tissue markers

**Women with DCIS on BX**

- Pre- or post Menopausal
- EGFR+ or Her2+ DCIS

**Tissue used for marker analysis (“Pre-treatment”)**

**Randomize**

**Lapatinib (1000mg) (N=30)**

**Placebo (N=30)**

**Surgery**

**Tissue used for marker analysis (“Post-treatment”)**

- 2-6 weeks

**LAPIS Trial (LAPatinib for In Situ Breast Cancer)**

Being conducted at BCM, DFCI, WRAMC, Georgetown University, M.D. Anderson, Mayo Clinic

Supported by the SPORE Grant and a grant from the Breast Cancer Research Foundation
Ongoing and Planned Preoperative Studies for DCIS

- Chloroquine - George Mason
- Vorinostat - UCSF
- Metformin
- Long list potential possibilities
Summary & Conclusions

• Preoperative therapy paradigm has moved into DCIS
• May allow for more rapid identification of useful alternative pharmacologic interventions
• Sets stage for potential for observation in select patients without further local therapy
## Trastuzumab for DCIS Trial

**HER2 Correlated With Grade**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total</th>
<th>Percent</th>
<th>Percent HER2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>38%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>56%</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>ER Status</td>
<td>Number (Percent)</td>
<td>Percent HER2+</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>54 (81%)</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>13 (19%)</td>
<td>62%</td>
<td></td>
</tr>
</tbody>
</table>
Development of HER2 Peptide Specific CD4 T cell Response

- Infg ELISPOT PBMC incubated with HER2 peptides before and after trastuzumab
- Suggests that treatment induces ADCC and that antigen released primes HER2 specific CD4 T Cells

1 of 12 patients
NSABP HER2+ DCIS Protocol

• Phase III trial of Lumpectomy + RT +/- trastuzumab in patients with HER2+ DCIS

• Primary endpoint
  • Any cancer event

• Secondary endpoints
  • IBTR
  • Contralateral cancer
Rationale for using Trastuzumab in DCIS

• ER-negative DCIS
  – No systemic treatment options exist
  – About 50% of ER- DCIS cases overexpress HER2

• ER-positive DCIS
  – About 20% of ER+ cases overexpress HER2

Claus E et al. Exp Molec Pathol 70:303, 2001
HER2+ DCIS NSABP B-43

Using Trastuzumab as a Radiosensitizer

Melody Cobleigh, MD
Rationale for using Trastuzumab in combination w/ RT in DCIS

• Trastuzumab is a radiosensitizer in HER2 overexpressing cancer cells

• Trastuzumab does not radiosensitize cells which do not overexpress HER2
NSABP DCIS Trastuzumab Schema

N = 2,000 Patients

Radiation Therapy

Radiation Therapy + Trastuzumab

q3-week Trastuzumab × 2

Screened tested = 2000 patients
Accrual = 30%; 600 patients