Monthly Oncology Tumor Boards:
A Multidisciplinary Approach to Individualized Patient Care – Hormone Sensitive Breast Cancer
February 9, 2016

Michael Berry, MD
The University of Tennessee Health Science Center/The West Clinic

Lee Schwartzberg, MD
The University of Tennessee Health Science Center/The West Clinic

Moderated by Shannon Ryan
NCCN, Conferences and Meetings Department

This activity is supported by educational grants from BTG; Bristol-Myers Squibb; Celgene Corporation; Genomic Health, Inc.; Lilly; Merck; Novartis Oncology; Prometheus Laboratories; Spectrum Pharmaceuticals, and by a grant from AstraZeneca, and an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

Faculty Biography

Michael Berry, MD is Department Chairman and Surgeon at The West Clinic Comprehensive Breast Center and Clinical Assistant Professor at The University of Tennessee Health Science Center in Memphis, Tennessee.

Lee Schwartzberg, MD is Professor of Medicine and Division Chief of Hematology/Oncology at The University of Tennessee Health Science Center and is the Executive Director of the West Cancer Center and Medical Director at The West Clinic in Memphis, Tennessee.
Case # 1

- 34 yo premenopausal white female noticed a lump in her left breast while camping. Lump is hard, nonmobile and nonpainful.
- Saw NP and had US with shadowing at 1 o'clock. Seen by general surgeon and biopsy done
- Biopsy: grade 2 infiltrating ductal cancer, ER+90%, PR+90%, HER2 2+ by IHC, FISH pending
- PMHx: Hypothyroidism, Hypertension, Gestational diabetes; Cholecystectomy
- Gyn Hx; G4P2, 18 weeks pregnant on OCP
- Social Hx: Nurse, Married, 12 pack-year smoking hx, none in 5 years

Case # 1

- Physical exam: 4.5 x 3.5 mobile mass at 2 o’clock. No lymphadenopathy
- ECHO EF 60-65%
- Genetic testing: Multigene panel negative
- Patient wishes breast conservation
- FISH + for HER2 amplification
Surgery in Pregnant Women

- Modern anesthetic agents very safe in the setting of pregnancy
- General concerns regarding anesthesia on pregnant patient
  - 1st trimester - organogenesis
  - 2nd trimester - safest time to operate
  - 3rd trimester - premature labor
SLN Biopsy in Pregnant Women

- 25 cN0 patients had SNBx when pregnant
  - 8 (1st trim.), 9 (2nd trim.) and 8 (3rd trim.)
  - 16 TC-99 alone, 7 meth. blue alone and 2 ? method
  - Isosulfan blue does not have FDA clearance for pregnancy
  - 24/25 live born infants without complications, 1/25 with cleft palate (maternal risk factors)
  - SLN biopsy accurate and safe in pregnant pop.


Breast Cancer in Pregnancy

- A fairly rare event, but increasing as age of pregnancy gets later (up to 36/100,000)
- Historically was considered to convey a poor prognosis in era before modern adjuvant rx
- Generally higher grade and advanced stage at diagnosis
- No randomized trials
Breast Cancer in Pregnancy: Recent studies

- Single institution (MDACC) case control study
- Prospective registry
- N=75 affected
- Published with 16 yr f/u 2013

- Amant F, et. al 2013
- Multinational European registry
- Prospective and retroactive
- 2003-2011

Clinical Pathologic Variables: European registry

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pregnant Patients (n = 311)</th>
<th>Nonpregnant Patients (n = 860)</th>
<th>Missing Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>104</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>177</td>
<td>339</td>
<td>46.1</td>
</tr>
<tr>
<td>3</td>
<td>85</td>
<td>277</td>
<td>25.5</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>66</td>
<td>5.0</td>
</tr>
<tr>
<td>2</td>
<td>107</td>
<td>307</td>
<td>32.3</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>76.2</td>
<td>5.65</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDC</td>
<td>39.4</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td>ILC</td>
<td>3</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>ER and/or PR positive</td>
<td>464</td>
<td>39.5</td>
<td>12</td>
</tr>
<tr>
<td>HER2 positive</td>
<td>31.9</td>
<td>17.9</td>
<td>12</td>
</tr>
<tr>
<td>HER2 negative</td>
<td>37.5</td>
<td>15.1</td>
<td>4</td>
</tr>
</tbody>
</table>

Pregnant patients:
- Higher grade,
- Higher stage,
- Less ER+, more TN

*NOTE: Descriptive statistics are reported after imputation of missing values.
*Abbreviations: AJCC, American Joint Committee on Cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor 2; ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; PR, progesterone receptor.
Registry results

DFS: HR Pregnancy 1.34 (0.93-1.91, p=.14)
OS: HR Pregnancy 1.19 (0.73-1.93, p=.51)

Amant F, et. al JCO 2013

A: DFS, B: OS

Single Institution Cohort Study

Pregnancy pts Did better!

Litton J, Oncologist 2013
Chemotherapy during pregnancy

- Anthracyclines, cyclophosphamide (5 FU) safe during 2nd and 3rd trimester
- Taxanes not sufficiently studied
- Trastuzumab contraindicated
  - Oligohydramnios
  - Fetal effects
Case #1

- Completing AC chemotherapy, every 3 weeks x 4
-Clinically responding to therapy with good partial response to AC
-Plan for adjuvant paclitaxel/trastuzumab followed by a year of trastuzumab after surgery
What is the optimal adjuvant endocrine therapy in this patient?
Endocrine Therapy: Tamoxifen or OFS/AI?

SOFT Trial: Efficacy Outcomes for OFS + Exemestane vs Tamoxifen Alone

<table>
<thead>
<tr>
<th>5-Yr Outcome, %</th>
<th>OFS + Exemestane</th>
<th>Tamoxifen Alone</th>
<th>Risk Reduction</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>89.0</td>
<td>84.7</td>
<td>32</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>DDFS</td>
<td>93.0</td>
<td>90.7</td>
<td>29</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>FBC</td>
<td>90.9</td>
<td>86.4</td>
<td>36</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>OS</td>
<td>95.3</td>
<td>95.1</td>
<td>3</td>
<td>NS</td>
</tr>
</tbody>
</table>


Dual Therapy in SOFT: 5-Yr Breast Cancer–Free Interval With and Without Chemotherapy

<table>
<thead>
<tr>
<th>Regimen, %</th>
<th>No Chemotherapy</th>
<th>Chemotherapy</th>
<th>Women &lt; 35 Yrs of Age (94% Received Chemo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-Yr Breast</td>
<td>Relative</td>
<td>5-Yr Breast</td>
</tr>
<tr>
<td></td>
<td>Cancer Incidence</td>
<td>Improvement</td>
<td>Cancer Incidence</td>
</tr>
<tr>
<td>Tam</td>
<td>4.2</td>
<td>22.0</td>
<td>32.3</td>
</tr>
<tr>
<td>OFS + Tam</td>
<td>4.9</td>
<td>5</td>
<td>17.5</td>
</tr>
<tr>
<td>OFS + AI</td>
<td>2.9</td>
<td>41</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>16.6</td>
<td>---</td>
<td>16.6</td>
</tr>
</tbody>
</table>

- Higher-risk pts received chemotherapy and benefited from its addition to OFS
- Pts who did not receive chemotherapy had such a low baseline risk that efficacy is difficult to assess

Case #2

- 60 y/o obese WF
- Menarche 16 y/o, G4 P4, menopause 45 y/o
- BCP X 3yrs, no HRT
- PMHx: bipolar, hypothyroidism
- FHx: neg.

Case #2

- PE: RB, 10:00, 2.3 X 2.0cm mobile mass, cN0
- Mam: RB, 10:00, 2.6 X 1.8 ill-defined stellate mass (BIRADS 4)
- Sono: RB, 10:00, 2.4 X 2.0 X 1.6 ill-defined hypo echoic irregularly shaped mass with posterior shadowing (BIRADS 4)
- Core biopsied
Case #2

• Path: IDC, Gr 1, ER=100%, PR=100%, Her-2=neg. (IHC), Ki-67=10%
• cStage IIA (cT2 cN0 cM0)
• Large breast amenable to breast conserving surgery which pt. desired

Margins in Breast Conserving Therapy for Infiltrating Carcinoma

• SSO and ASTRO Consensus Guidelines for margins in Stage I & II cancer patients undergoing breast conserving surgery and WBI (2014)
• Meta-analysis on ~28,000 pts. with min. median follow up of 4 years in studies from 1965-2013
• No neo-adj. or pure DCIS in these guidelines
Importance of Margins in Breast Conserving Therapy

- **Pos. margin** = ink on tumor (inv. or DCIS) at edge of resected tissue in breast conserving surgery
  - 2 fold increase in IBTR (regardless of XRT boost, ca. biology or systemic therapy)
- **Neg. margin** = NO ink on tumor at edge of resected tissue
  - Lowest risk of IBTR
  - Increase width doesn’t lower risk

J Clin Oncol. 2014 May 10;32(14):1507-15

Importance of Margins in Breast Conserving Therapy

- Systemic therapy lowers IBTR
  - If not received, there is no evidence that wider margins add benefit compared with negative margins
- Women <40 y/o have increased IBTR regardless of width of negative margin
- EIC has no increased risk of IBTR if neg. margins

J Clin Oncol. 2014 May 10;32(14):1507-15
ACOSOG Z0011

**Clinically Negative Patients 1-2 Positive SNs by H & E**

**Lumpectomy + Breast XRT**

**Randomization**

**Completion Axillary Node Dissection (n = 445)**

**No Further Surgery (n = 446)**

**N = 420**

**N = 436**

Included in Primary Analysis


### ACOSOG Z0011

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SNB Alone</th>
<th>Completion AND</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional Positive Nodes on AND</td>
<td>N/A</td>
<td>27.3%</td>
<td></td>
</tr>
<tr>
<td>5-Year In-Breast Recurrence</td>
<td>??</td>
<td>97 pts</td>
<td></td>
</tr>
<tr>
<td>5-Year Axillary Nodal Recurrence</td>
<td>2.1%</td>
<td>3.7%</td>
<td>0.16</td>
</tr>
<tr>
<td>5-Year Overall Survival</td>
<td>92.5%</td>
<td>91.8%</td>
<td>HR: 0.87</td>
</tr>
<tr>
<td>(90-95.1)</td>
<td>(89.1-94.5)</td>
<td>.25</td>
<td></td>
</tr>
<tr>
<td>5-Year DFS</td>
<td>83.9%</td>
<td>82.2%</td>
<td>HR: 0.88</td>
</tr>
<tr>
<td>(80.2-87.9)</td>
<td>(78.3-86.3)</td>
<td>.14</td>
<td></td>
</tr>
</tbody>
</table>

ACOSOG Z0011: Conclusions

- T1-2, cN0 BC pts undergoing lumpectomy and XRT
  - cN0 = non-palpable
- If 1-2 SLN+ for macromets., no ALND or additional radiation fields needed
- No difference in L/R recur, DFS or OS in ALND vs No ALND group (6.3 yr F/U)


Recommendations for SLN+

- SLN-, don’t do ALND
- SLN+ (micromets), don’t do ALND whether lumpectomy or mastectomy
  - Don’t do routine IHC to find micromets
- SLN+ (macromets), don’t do ALND if only 1-2 + nodes, having lumpectomy and receiving WBI and systemic tx
  - 2/3 of all node + pts. have only 1-2 nodes pos.
When is ALND required?

- cN pos
- IBC
- >2 + SLN (macromet)
- Gross extra-nodal tumor extension
- Resid. palp nodes after SLN bx
- SLN + (macromet) having mastectomy
- SLN + (macromet) not receiving XRT or systemic tx

Case #2

- Surgery: partial mastectomy with SLN bx converted to ALND. Several (4) nodes clinically pos. during surgery led to conversion
- Path:
  - Breast: IDC 3.2cm, biology unchanged, LVI+, EIC+, closest margins 2mm for IDC and 1mm for DCIS others widely clear
  - LN: 5/11 pos. nodes, largest 1.8cm with extra-nodal extension
  - pStage IIIA (pT2 pN2 M0)
Results: For Any Recurrence Score the Rate of Distant Recurrence Increases with the Number of Positive Nodes

Dowsett et al., SABCS 2008, Abstract # 53
Does chemotherapy help all node positive patients? Biology may play a larger role than anatomy

Case # 3

- 79 yo WF presented in 2009 with breast mass
- Core biopsy showed ILC with ductal component, grade 2 ER+PR+Her2-. Palpable axillary LN +
- Underwent bilat mastectomies:
  - Left 7.4 cm infiltrating ductal cancer with associated comedo DCIS 13/19 LNs positive
  - Right, 2 cm intracystic papillary cancer with negative margins, 6 LNs negative
  - PET/CT scan internal mammary nodes +

Intracystic Papillary Carcinoma (IPC)

- <1% of breast cancers
- Pure form or associated with IDC or DCIS
- Dx: Micro: IHC for absence of intact myoepithelial cell layer
  - Present=benign
  - Absent=malignant

Intracystic Papillary Carcinoma (IPC)

• Treatment:
  – Pure form: surgical resection alone, no data to support any additional therapy
  – Associated with IDC or DCIS: target adjuvant XRT or endocrine based on this component

• Prognosis:
  – Pure form: Excellent with exc. alone
  – Associated IDC or DCIS: determines prognosis


Case #3

• Adjuvant TC X 6
• RT to chest wall, SCLNs and IM LNs
• Began letrozole 10/09
• Tolerated it well with good adherence
• 11/15 presented with mild-mod pain in lower back x 2 months, not precipitated by trauma or movement, slowly worse
• Obtained laboratory showed increase tumor marker
Case #3

• Bone scan: Extensive osseous disease in calvarium, multiple levels thoracic and lumbar spine, most pronounced in L1, pelvic, L distal humerus
• CT CAP: No definite disease, questionable lesion L1, no vertebral compression
• CA15-3 974; CEA 99

What 1st line therapy should the patient begin?
Double blind Phase 3

**Primary endpoint: PFS**
PALOMA-3: Efficacy and safety

Turner NC, et. al. NEJM 2015

Case #3

- Letrozole D/C
- Began Fulvestrant/Palbociclib 12/15
- Also began denosumab
- Good tolerance; mild neutropenia
- Initial tumor markers at 6 weeks were CA15-3 686, CEA 65
Three Identical International, Randomized, Double-Blind, Active-Controlled Trials

**Enrollment Criteria**
- Adults with breast, prostate, or other solid tumors and bone metastases or multiple myeloma
- No current or prior IV bisphosphonate administration for treatment of bone metastases

**Denosumab 120 mg SC and Placebo IV* every 4 weeks (N = 2862)**

**Zoledronic Acid 4 mg IV* and Placebo SC every 4 weeks (N = 2861)**

**Supplemental Calcium and Vitamin D Recommended**

**1° Endpoint**
- Time to first on-study SRE (non-inferiority)

**2° Endpoints**
- Time to first on-study SRE (superiority)
- Time to first and subsequent on-study SRE (superiority)

**Primary Endpoint: Time to First On-Study SRE**

- Breast Cancer (N = 2046)
  - HR 0.82 (95% CI: 0.71, 0.95)
  - \( P = 0.0001 \) (Non-inferiority)
  - \( P = 0.01 \) (Superiority)

- Prostate Cancer (N = 1901)
  - HR 0.82 (95% CI: 0.71, 0.95)
  - \( P = 0.0002 \) (Non-inferiority)
  - \( P = 0.0008 \) (Superiority)

- Other Solid Tumors or Multiple Myeloma (N = 1776)
  - HR 0.84 (95% CI: 0.71, 0.98)
  - \( P = 0.0007 \) (Non-inferiority)
  - \( P = 0.06 \) (Superiority)

* All data come from the primary analysis phase of these studies

Incremental Benefits in Breast Cancer

64% risk of skeletal complication with **no bisphosphonate** at 2 yrs

Approx 33% risk reduction with **pamidronate**

Further 20% risk reduction with **zoledronic acid**

Additional 18% risk reduction with **denosumab**

Endocrine Therapy for Recurrent or Stage IV Disease

Premenopausal Patients with hormone-receptor positive disease should have ovarian ablation/suppression and follow premenopausal guidelines:

- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Selective estrogen-receptor modulator ( exemestane)
- Exemestane + exemestane
- Paclitaxel + letrozole
- Paclitaxel + fulvestrant (category 1)
- Fulvestrant
- Tamoxifen or exemestane
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

1 A combination of exemestane with letrozole may be considered for patients who meet the eligibility criteria for BOlBO-2 (progressed within 12 mo or on menopausal AIs) and are on tamoxifen
2 Paclitaxel in combination with exemestane may be considered as a first-line therapy for premenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer.
3 For postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH agonist, with hormone-receptor positive and HER2-negative metastatic breast cancer that has progressed or is resistant to endocrine therapy, administration of chemotherapy and/or endocrine therapy memebrands demonstrated that the addition of fulvestrant to exemestane resulted in prolongation of time to progression. Randomized trials suggested that patients without prior adjuvant tamoxifen and more than 12 years since diagnosis experienced the greatest benefit. Two studies with similar design (FULBET and BO205A) demonstrated no advantage in time to progression with the addition of fulvestrant to exemestane.

Clinical Note: NCCN believes that the best management of metastatic breast cancer is a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Member Institutions

Copyright 2016©, National Comprehensive Cancer Network®. All rights reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.