Breast Cancer: Medical Oncology Update for the Primary Care Physician

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Disclosures

- I am a speaker for Genomic Health & Janssen Pharmaceuticals
- I will not be speaking on any off label uses
Outline

- Brief Overview of Breast Cancer
- Staging of Breast Cancer
- Clinical Trials update
- MA.17R data (AI 10 years)
- CALGB 40603/GeparSixto data (platinum triple negative)
- ABCSG-18 data (denosumab adjuvantly)
- Tryphaena data (Her2/neu + neoadjuvant treatment)
- Common questions from patients

Breast Cancer is a Global Problem!
1.4 Million women will get a diagnosis of breast cancer 
460,000 will die from breast cancer: 2014

Back to basics...

- Breast Cancer is the most common cancer amongst women worldwide
- Accounts for 23% of all cancer diagnosed amongst women
- 2nd leading cause of death in from cancer in women
- Main cause of death in women aged 40-49
- In Western countries, 90% of the time disease is localized
- Currently more than 2.9 million breast cancer survivors in the United States
- 1/8 women will develop invasive breast cancer in their lifetime
**More basics…**

- Infiltrating or Invasive Ductal Carcinoma is the most common breast cancer subtype and comprises 70-80% of all cases.
- Factors to consider when staging a breast cancer patient:
  - ER (Estrogen) PR (Progestosterone) Her2/neu status
  - Tumor size
  - Number of positive nodes
  - Histology or nuclear grade
  - Gene expression profiles (Oncotype, Mammoprint, etc.)
Risk factors:
Sporadic vs. Hereditary

- Sporadic: 90%
- Hereditary: 5-10%

- Sporadic
- Hereditary
Hereditary Breast Cancer

50 year old school teacher comes to the office because her sister (43 years) is diagnosed with breast cancer. Her mother had breast cancer at the age of 70.

One of her paternal aunts had ovarian cancer and another aunt had breast cancer at the age of 41.

BRCA 1

- Located on chromosome 17 (17q12-23)
- Tumor suppressor gene
- Maintain genomic stability
- Repair of double stranded DNA
- Breast cancer, ovarian cancer
- ?colon, stomach, leukemias and lymphomas
- Higher penetrance in females

BRCA 2

- Chromosome 13 (13q12-13)
- Tumor suppressor gene
- Maintain genomic stability
- Repair of double stranded DNA
- Breast cancer, ovarian cancer, Prostate, pancreas, stomach, Gall bladder, melanoma
- Higher penetrance in males
Sporadic Breast Cancer; and or woman with high risk

<table>
<thead>
<tr>
<th>Screening</th>
<th>Starts at 40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life style modification</td>
<td>Exercise and diet</td>
</tr>
<tr>
<td>Chemo-prevention</td>
<td>Tamoxifen, raloxifene, Anastrazole and Exemestane</td>
</tr>
<tr>
<td>Prophylactic mastectomy</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Prophylactic oophorectomy</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

NSABP P-1, NSABP P-2, NEJM 2011 SABCS 2013, American Cancer Society 2014

Brief Overview of Updates in Breast Cancer

- 4 new studies have changed the way many Oncologists have treated breast cancer in the past 2 years
- Will touch on all 4 of them briefly
  - MA17.R, data presented at ASCO 2016 extending endocrine therapy to 10 years as opposed to 5 (hormone positive, early stage patients)
  - CALGB40603- Giving neoadjuvant carboplatin in triple negative breast cancers to improve pCR recently presented at SABC 2015
  - ABCSG-18- Giving Denosumab in adjuvant, post-menopausal women to decrease fractures and ? Increase DFS
  - Tryphaena- Giving Perjeta(pertuzumab) in T2 +/- N1, Her2/neu positive patients to improve pCR in neoadjuvant setting
Breast Cancer Staging

Table 1 (continued)

| ST4 |

Prognostic features ("traditional")

- Number of positive axillary nodes
- Tumor size
- Estrogen/progesterone receptors
- Histologic and Nuclear grade
- Lymphatic and vascular invasion
- Histologic tumor type
- HER2/neu overexpression
Hierarchical clustering of primary breast tumors using the "intrinsic" subset of genes


Overall survival analysis of breast cancer patients stratified by gene expression-based subtypes

Breast Cancer - Lymph Node Positive

Lymph Node
- LN +
  - Her2/neu -
  - Her2/neu +

Decision?
- Chemo (Risk Stratify)
- Chemo + Trastuzumab +/− pertuzumab

Breast Cancer Lymph Node Negative

LN
- LN -
  - HR +
  - HR -

Hormone
- HR +
- HR -

Her2/neu
- Her2/neu +
- Her2/neu -

Consider Chemo + Trastuzumab +/− pertuzumab
Adjuvant endocrine therapy
Chemo based on risk stratification
Chemo + Trastuzumab +/− pertuzumab in high risk
Consider Chemotherapy
Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years


Study Design

Primary Breast Cancer Completed 4.5-6 years of AI or Tamoxifen

Baseline
1918 women enrolled

Time 5 years
Side effects between two groups almost identical

Significance met for bone fracture, new onset osteoporosis & elevated alkaline phosphatase level

Small, but statistical significant change in disease free survival noted

No change in overall survival when comparing the two
How should we react?

- Small but important subgroup that there is a continuing risk of relapse up to at least 15 years after diagnosis
- A small (3.2%) group have improved DFS with 10 years compared with 5

- BUT...
- A reduction in contralateral breast cancer contributes significantly to the DFS benefit
- Difference is only 1.1% for distant recurrence
- No survival benefit
- From NEJM- The extension of treatment with an adjuvant aromatase inhibitor to 10 years resulted in significantly higher rates of disease-free survival and a lower incidence of contralateral breast cancer than those with placebo, but the rate of overall survival was not higher with the aromatase inhibitor than with placebo.
Oncotype Dx: Recurrence Score

- Low Risk Group
- Intermediate Risk Group
- High Risk Group

Recurrence Score as a Continuous Predictor

- Low Risk Group
- Intermediate Risk Group
- High Risk Group

Chance of recurrence of in 10 years is 8%

No chemotherapy
Anti-estrogen
Chemotherapy

Paik et al, SABCS 2003, NEJM 2004
How should we react?

- Need more data! Oncotype, Mammoprint, genomic tests (Breast Cancer Index) so that the great majority of patients who don’t need prolonged therapy can be identified
- Data does not justify telling all patients to continue letrozole or any other AI to 10 years (or beyond)
- High risk patients with early side effects, data can be discussed and used to help make decisions

Triple Negative Breast Cancer

- Triple negative breast cancer is a very difficult to treat cancer
- Accounts for 20% of breast cancers worldwide
- More commonly in women under 40
- Risk factors include BRCA mutation, African American, pre-menopausal women
- Worse prognosis then other breast cancer subtypes
- Worse overall survival, breast cancer specific survival, and a dramatic increase in death within 2 years of diagnosis
GeparSixto Trial

- GeparSixto complicated trial, do not need to go into details
- Patients with TNBC, difference in 3 year DFS between carboplatin and no carboplatin (85.8% versus 76.1%) p= 0.0325
- Showed a pCR rate of 36.9% without carboplatin, 43.7% with carboplatin
- (no statistical significance in pCR rates)
Showed pCR were increased
- No association yet between Event free or Overall survival, however it was not powered to meet this outcome
- 3 Year Event free survival was 86% for patients who achieved pCR, and 62% for those that did not
- The 3 year overall survival rate was 93% and 73%, respectively
- Data difficult to interpret as there was a bevacizumab (Avastin) arm

Based on data, many are incorporating in neoadjuvant treatment options
- pCR = OS?
- More data coming
- Patients with T2 tumors (greater than 2 cm) or node positive disease should strongly consider neoadjuvant treatment with a carboplatin regimen
- Many are getting paclitaxel weekly with Carboplatin q3 weeks, followed by dd AC
- The “answer” is coming with clinical trials that are powered for this conclusion...
Adjuvant endocrine therapy compromises health in pre and postmenopausal breast cancer patients

Fractures are a side effect of Aromatase Inhibitors (AI's)

Investigate the effects of adjuvant anti-RNAK-lignand Denosumab in postmenopausal patients with early stage BC receiving an AI

Primary Breast Cancer On AI

Denosumab 60 mg every 6 months for 3 years

Placebo

Baseline
3425 women enrolled

Time 5 years
Results

- No difference between Denosumab and Placebo with respect to incidence of adverse events (1366 vs 1344)
- No difference in serious adverse events (521 vs 511)
- No ONJ observed
- Increased BMD of lumbar spine, total hip, and femoral neck at 36 months
- Observed reduction in fractures similar in prognostic patient subgroups, i.e. those with normal bone health at baseline and in patients that were already osteopenic

Results

- 50% Fewer fractures
- 18% fewer relapses (Reduction is near significance, HR=0.816 and p=0.051)
- More benefit in tumors greater than 2 cm in size
- Those at the early start of treatment
- Those tumors with high receptor density
Incorporation into Practice

- Discussed at first visit
- Baseline DEXA ordered
- Discuss trial results
- Informed decision with patient
- Some are offering to all patients, irrespective of their bone health status

Her2/neu positive breast cancer

- Amplification or overexpression of the human epidermal growth factor 2 (HER2/neu) is present in about 18-20 of breast cancers
- Women with early stage breast cancer that meet criteria are treated with chemotherapy + Trastuzumab in early stage breast cancer
- New frontier- adding a new drug
- Addition of Pertuzumab is designed to overcome Trastuzumab resistance caused by formation of HER2:HER3 heterodimers
Tryphaena Trial

The TRYPHAENA trial evaluated PERJETA®-based neoadjuvant treatment with and without an anthracycline

An additional Phase 2 neoadjuvant study1,2

- 225 patients with locally advanced, operable, or inflammatory HER2+ breast cancer (T2-4a)
- Designed primarily to assess cardiac safety; all arms included PERJETA
- All treatments administered in 3-week cycles

**TRYPHAENA trial overview1,2**

<table>
<thead>
<tr>
<th>Neoadjuvant regimen1</th>
<th>Adjuvant regimen</th>
<th>Incidence of 0%</th>
<th>Incidence of symptomatic LVSD (CHF) %</th>
<th>PCR (0% complete year of treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles 1-3</td>
<td>PERJETA + TCH</td>
<td>2.6</td>
<td>0.0</td>
<td>63.5 [44.9-79.3]</td>
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<tr>
<td>Cycles 4-6</td>
<td>HER2</td>
<td>Completing 1 year of treatment</td>
<td></td>
<td></td>
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<tr>
<td>n=76</td>
<td>PERJETA + Herceptin (trastuzumab) + docetaxel</td>
<td>4.0</td>
<td>2.7</td>
<td>54.7 [47.7-61.2]</td>
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<tr>
<td>n=75</td>
<td>FEC</td>
<td>Completing 1 year of treatment</td>
<td></td>
<td></td>
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<tr>
<td>n=72</td>
<td>PERJETA + Herceptin</td>
<td>5.6</td>
<td>0.0</td>
<td>56.2 [44.1-67.1]</td>
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Her2/neu + disease

Percent of patients in subgroups who achieved pCR in breast and nodes1

- In the hormone receptor-positive subgroup
  - PERJETA + TCH: 47.5% (95% CI: 31.5-63.9)
  - FEC followed by PERJETA + Herceptin = docetaxel: 45.7% (95% CI: 28.8-63.4)
  - PERJETA = Herceptin + FEC followed by PERJETA + Herceptin = docetaxel: 41.0% (95% CI: 25.6-57.9)

- In the hormone receptor-negative subgroup
  - PERJETA + TCH: 81.1% (95% CI: 64.8-92.0)
  - FEC followed by PERJETA + Herceptin = docetaxel: 62.5% (95% CI: 45.8-77.3)
  - PERJETA + Herceptin = FEC followed by PERJETA + Herceptin = docetaxel: 73.5% (95% CI: 55.8-87.1)

*TRYPHAENA is referred to as “Study 3” in the full PERJETA Prescribing Information.*
Conclusions on Tryphaena

- Now standard of care in T2 or larger, N1 or greater, neoadjuvant treatment option
- Low incidence of cardiac events <5%
- High pCR rate
- Not powered to evaluate overall survival

Story of the two women

- 54 year old woman with ER/PR positive, Her-2 positive, stage III breast cancer
- At the time of diagnosis, had liver and bone mets

2005, West Virginia University
Morgantown
Before Treatment

After chemotherapy with trastuzumab

Brufsky A, Abraham J et al. SABC 2004

How she did well for many years?

Trastuzumab
Pertuzumab

Lapatinib
Neratinib

Targeted therapies: Her-2 pathway
Stepwise Improvement in Outcomes for Early Stage Breast Cancer
Potential Incremental Improvements through Clinical Trials

Local Therapy Only

Risk of Recurrence

- + Hormonal Therapy (Tamoxifen)
- + Hormonal Therapy (Aromatase Inhibitor)
- + Chemotherapy
- + Chemotherapy (+ Taxane)
- + Chemotherapy (Dose Dense)
- + Trastuzumab
- ? + Bisphosphonates
- ? + COX2 Inhib
- ? + Vaccine

Common Patient Questions
Q: What is the association, if any, between exemestane (Aromasin) and heart problems? Why does this appear in the list of side effects?

A: There is no dramatic risks of heart disease with exemestane. However, there can be increases in cholesterol and in blood pressure with aromatase inhibitors. Continue to follow up with your primary physician to have your lipids and blood pressure monitored.

Q: Is it safe to eat soy if I have Estrogen Positive Breast Cancer?

A: There no data that eating soy affects breast cancer. The phytoestrogens found in soy are not known to have any physiological effects. The various soy preparations frequently used in foods are also not known to have any effects on breast cancer patients. There are no firm data that eating soy, or other specific foods, will increase risk of cancer recurrence. Recommend a healthy plant based diet that includes fruits, veggies, and meat in moderation.
Q: What is the standard of care after treatment for triple-negative breast cancer?

A: Following completion of active treatment for any breast cancer survivor, follow-up care includes regular visits with your providers, which should include physical examination and annual mammogram.

For a breast cancer survivor who is doing well and feeling well, there is no role for routine blood tests or body imaging.

There are new agents being evaluated in clinical trials to try to help outcomes in people with triple negative breast cancer, and you can talk to your provider about whether such a trial is available.

What can I do about these night sweats and hot flashes????

A: We hope they fade over time. There are newer SSRI’s such as venlafaxine (Effexor) that can reduce symptoms. Prozac and Paxil also do, however we have to be careful with the interaction with Tamoxifen.

There is also recent data in JCO (March 28th 2016) that acupuncture was associated with fewer “climacteric” symptoms and a higher quality of life in the vasomotor, physical, and psychosocial dimensions.
Thank you!

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