Hormone Receptor Positive and HER2+ Breast Cancer

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Introduction

- Breast cancer update just for you
  - Hormone receptor positive disease
  - HER2+ disease
- Definitions (what you “need to know”)
- Treatment (how it’s different in each)
Definitions

- How do we talk about breast cancer from a medical perspective?
  - How do we classify breast cancer?
  - What are the different types?
- Why is this important?
  - Because they behave differently
  - And may be treated differently
Breast Cancer Histology

- Adenocarcinoma (gland forming)
  - Ductal more common than Lobular
  - Tubular, Mucinous, Anaplastic
  - Invasive vs non-invasive = “in situ”
- Other: lymphoma, sarcoma, melanoma
Breast Cancer Pathology

- Tumor size
- Grade of differentiation
  - Low = Grade I = well differentiated
  - Intermediate = Grade II
  - High = Grade III = poorly differentiated
- Lymph node involvement (___ of ___)
Pathology, cont’d

- Immunohistochemical staining for ER/PR
  - Estrogen receptor (ER)
  - Progesterone receptor (PR)
  - If either > 5-10% then considered hormone receptor positive

- Staining for HER2 …
Pathology, cont’d

- **IHC testing for HER2/neu expression**
  - 0 and 1+ = negative
  - 2+ = indeterminate $\rightarrow$ test by FISH
  - 3+ = positive

- **FISH testing for HER2 expression**
  - Negative, positive, or indeterminate
Sub-groups of breast cancer

- “Hormone receptor positive” (HRP)
- “Hormone receptor negative” (HRN)
- “HER2 positive” (HER2+)
- “Triple negative”
  - neither HER2+ nor HRP
Staging

- “TNM” system
  - Tumor size (in centimeters)
  - Nodal status
    - Negative ("lymph node negative")
    - Positive: 1-4 LN vs >4 LN
  - Metastatic disease
    - Spread beyond the breast and draining lymph nodes
Staging

American Joint Committee on Cancer
Breast Cancer Staging

Primary Tumor (T)

T1: In situ (e.g., ductal carcinoma in situ)
T2: 2 cm or less in greatest dimension
T3: Larger than 2 cm and less than or equal to 7 cm in greatest dimension
T4: Greater than 7 cm in greatest dimension
T4a: Tumor directly invades chest wall or Cooper's ligament
T4b: Metastasis to skin

Distant Metastases (M)

M0: No distant metastases
M1: Metastases to any site

Staging, Stage Grouping, and Clinical Planning Summary

Stage I:
Stage II:
Stage III:
Stage IV:

Note: Staging and classification are based on clinical examination and imaging studies.
Staging
“Whoa—way too much information!”
Staging

- **TNM**
  - Stage 0 = carcinoma in situ (DCIS or LCIS)
  - Stage 1 = tumors under 2cm
  - Stage 2 = small tumors with involved nodes, or larger tumors without nodes
  - Stage 3 = large tumors and involved nodes
  - Stage 4 = metastatic disease
Limits of Staging

- Doesn’t take into account (currently)
  - Hormone receptor status
  - HER2neu expression
  - Menopausal status

- But these impact treatment decisions!
Clinical Staging

- DCIS/LCIS (Stage 0)
- Tumors <1cm versus >2cm
- Lymph node involvement
- Hormone receptor status
- HER2neu expression
- Menopausal status
Clinical Staging -> Impacts

Treatment

- DCIS/LCIS (Stage 0) -> “not cancer”
- Tumors $< 1\text{cm}$ versus $> 2\text{cm}$ -> chemo?
- Lymph node involvement -> (chemo)
- Hormone receptor status -> anti-estrogen tx
- HER2neu expression -> Herceptin
- Menopausal status -> (subtleties)
Adjuvant vs Metastatic

- **Adjuvant**
  - After surgery or other treatment with curative intent (such as chemotherapy)

- **Neo-adjuvant**
  - Before surgery or other treatment with curative intent (such as chemotherapy)

- **Metastatic**
  - Spread beyond
Adjuvant vs Metastatic, cont’d

- **Adjuvant**
  - All treatment with curative intent
  - Used in patients with Stage 1-3 disease
- **Neo-adjuvant**
  - Also with curative intent
- **Metastatic = Stage 4**
  - Treatment is palliative, not curative
Treatment

- Why do different people get different treatment for breast cancer?
- Which treatment to pursue impacted by
  - Stage (TNM 0, 1 – 4)
  - Type (HRP, HER2 expression)
  - Other factors that impact risk of recurrence (such as menopause)
Treatment

Treatment in the Adjuvant setting
- Hormone Receptor Positive disease
- HER2+ disease

Treatment in the Metastatic setting
- Hormone Receptor Positive disease
- HER2+ disease
Treatment in Adjuvant Setting

- For patients with stage (0), 1-3
- Treatment with curative intent
- “Multimodality”
- Different for patients with
  - HER2+
  - HRP = hormone receptor positive
Treatment

- Multidisciplinary approach
  - Surgery
  - Radiation
  - Systemic therapy
    - Anti-estrogen if HRP
    - Chemotherapy

- Who needs which treatment?
WHEN DO YOU NEED IT?
Treatment

- “Local” – can be curative by itself
  - Surgery
  - Radiation
- “Systemic” – can be added to increase cure
  - Chemotherapy
  - *Anti-HER2 directed therapy (if HER2+)
  - Anti-estrogen therapy (if HRP)
Adjuvant Treatment - Systemic

- Anti-estrogen therapy
  - For anyone with hormone receptor positive (HRP) disease
    - Tamoxifen in pre- or post-menopausal
    - Aromatase Inhibitors only in post-mp
      - (evolving data for use in pre-mp women with ovarian shut down)
Anti-estrogen therapy - Updates

- For post menopausal women...
  - Aromatase Inhibitors with persuasive data over Tamoxifen for 5 years
    - Anastrozole = Arimidex
    - Letrozole = Femara
    - Exemestane = Aromasin
  - Now data to support 10 years
Anti-estrogen therapy – TAM vs AI

- Side effects (all):
  - Hot flashes, night sweats
  - Weight gain, depression
  - Vaginal dryness and sexual dysfnc
  - Low white count
  - Elevated liver enzymes
  - ?Cataracts, ?lipid abnl (esp with Tam?)
TAM vs. AI, (cont’d)

<table>
<thead>
<tr>
<th>TAM</th>
<th>AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 4% risk of VTE</td>
<td>1 - 2%</td>
</tr>
<tr>
<td>1 - 2% risk uterine ca (protects)</td>
<td>---</td>
</tr>
<tr>
<td>&lt;1% arthralgias (traditional)</td>
<td>(?worsens) 30-70% (more effective)</td>
</tr>
</tbody>
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Anti-estrogen therapy, (cont’d)

- Recommendations
  - Yearly Ophtho and GYN visits if on TAM
  - Baseline DEXA scan if on AI
  - Repeat (every 2 years) if DEXA abnormal with low threshold to use bisphosphonates
    - Fosamax or Actonel (pills)
    - Zometa IV (annually) or Prolia SQ (2x/yr)
Adjuvant Treatment - Systemic

- Chemotherapy
  - Who needs it?
Adjuvant Chemotherapy

- Based on risk of recurrence of cancer
  - Tumor size, nodal status
  - ER/PR/HER2
  - Grade, lymphovascular invasion
- Risks vs benefits
  - Age and performance status of patient
  - Menopausal status
Calculating Risk

- Norton rule of thumb
  - Uses only size and lymph node status
- Adjuvant!
  - On-line tool with multiple variables
- Oncotype Assay and Mammaprint
  - Genomic assays
Calculating Risk, (cont’d)

- Adjuvant!
- Computerized prognostic model for estimating risk of recurrence (and likely benefit from adjuvant therapy)
- From SEER database (Surveillance, Epidemiology and End Results program of NCI)
- www.adjuvantonline.com

Ravdin, et al, JCO 2001
Calculating Risk, (cont’d)

- **Oncotype DX assay**
  - Originally for LN-neg, HRP, post-menopausal women
  - Genomic assay performed on tissue itself
  - Used to see if chemotherapy likely to beneficial

- Categorizes into low, intermediate, or high risk
  - *Low risk* -> derive little benefit from chemotherapy
  - *High risk* -> derive significant benefit from chemo
  - *Intermediate risk* -> test not helpful

Fisher, et al, NEJM 2004
We Can Do It!
Treatment - Adjuvant

- Adjuvant chemotherapy recommended if risk of recurrence > 10%
  - Norton rule
  - Adjuvant! Online
  - High risk features
    - Triple negative
    - HER2+
Treatment – Adjuvant, (cont’d)

- If post-menopausal, HRP, HER2-neg, lymph node negative ➔
  - Offer chemo only if >2cm (or more)

- If pre-menopausal, HRP, HER2-neg, lymph node negative ➔
  - Offer chemo if >2cm
  - May also offer if >1cm and “high risk”
Treatment – Adjuvant, (cont’d)

- If post-mp, HRP, HER2-neg, LN neg ➔
  - Offer chemo only if >2cm
  - Or if Oncotype HIGH RISK at any size

- If pre-mp, HRP, HER2-neg, LN neg ➔
  - Offer chemo if >2cm
  - May also offer if >1cm and “high risk”
Treatment – Adjuvant, (cont’d)

- If HER2+, offer chemo if > 0.5cm
- If triple negative, offer chemo if > 0.5cm
- If lymph node positive, offer chemo
  - Oncotype now validated here
  - Now can spare some women with even lymph positive disease chemotherapy, if low risk Oncotype score
Adjuvant Chemotherapy

Which regimen?
- Not different based on hormone receptor status (HRP vs HRN)
- Although whether to pursue chemo at all may impact decision for chemo
- Very different if HER2+
Adjuvant Chemotherapy
- for NON-HER2 overexpressing

- “AC” = Adriamycin (Doxorubicin) + Cytoxan (Cyclophosphamide)
- “TC” = Taxotere (Docetaxel) + CTXN
- “ddAC/T” = dose dense AC followed by Taxol (Paclitaxel)
- TAC (toxic), ECF/FEC/FAC (Europe), CMF (elderly), many others…
Adjuvant Chemo, (cont’d)

- “AC” ⇔ “TC”
  - TC shown to be non-inferior to AC in lymph node pos and neg pts
  - But AC inferior to ddAC/T in LN+ pts
  - TC avoids cardiotoxicity of anthracycline

- “ddAC/T”
  - OS adv in high risk pts
  - Need to follow MUGA/echo -> cardio-onc

Jones et al, JCO 2009
Adjuvant Chemo
- in triple neg

- “Triple negative” = ER/PR/HER2 negative
- “Any of the above” regimens
- +/- Addition of Carboplatin
  - Phase II data promising
  - Await Phase III (large cooperative trial now)
Adjuvant Chemo
- in HER2+

- AC/TH – addition of Trastuzumab (Herceptin)
  - AC every 2 weeks x 4
  - T+H weekly x 12 (or every 2 weeks x 4)
  - Followed by completion of 1 year Trastuzumab

- In neo-adjuvant setting
  - “THP” = Taxotere, Herceptin, Perjeta
  - “TCHP” = all above with Carboplatin
Neo-adjuvant chemotherapy

- Given before curative intent (surgery)
  - To downstage
  - Allow surgical resection
  - Improve ability to get clean margins
  - Especially inflammatory breast cancer
  - Has never been shown to improve overall survival
Targeting the HER2 receptor

- HER2/neu is an EGFR (epidermal growth factor receptor)
- Constitutively turned ON => tumor growth
- Anti-HER2 directed therapy targets that very growth factor => to turn it off
  - Trastuzumab (Herceptin)
  - Pertuzumab (Perjeta)
Targeting the HER2 receptor

- Combination with dual anti-HER targets
  - Trastuzumab + Pertuzumab (synergistic)
  - Approved in the metastatic setting
  - Approved in the neoadjuvant setting
  - Being studied in the adjuvant setting
Adjuvant Treatment - timing

- Establish diagnosis of breast ca (biopsy)
- (Neo-adjuvant treatment)
- Definitive surgery
- (Adjuvant chemotherapy)
- (Adjuvant radiation therapy)
- (Anti-estrogen therapy)
Different presentations

- Not everyone is early stage at presentation
- Some patients diagnosed with metastatic disease at presentation
- Some patients go through all of above, and then develop metastatic disease despite having completed adjuvant treatment
Treatment in Metastatic Setting

- Palliative (not curative)
- Goal to improve quantity and quality life
  - Live longer
  - Feel better
- Paradigm shift
- “Less is more”
  - reduce toxicity without reducing efficacy
Sequential, single agent therapy in the metastatic setting

- More isn’t always better
- Use as few agents for as long as possible
- No studies to show combination therapy in metastatic setting has improved survival over sequential, single agent therapy
  - Except in HER2 overexpressing disease
    - Where combo of dual anti-HER2 synergistic
  - Or if need quick response
Treatment

- Treatment in the Adjuvant setting
  - Hormone Receptor Positive disease
  - HER2+ disease

- Treatment in the Metastatic setting
  - Hormone Receptor Positive disease
  - HER2+ disease
Treatment - Metastatic

- Extent of tumor burden
- Impending visceral crisis
- Symptomatic
- Hormone receptor positive
- HER2 positive
Treatment – Metastatic, (cont’d)

- If HRP, HER2-neg, and stable -> anti-estrogen tx

- If HER2-pos and needs chemo -> regimen containing anti-HER2 targeted therapy
  - “THP” or “TCHP”

- If HER2-neg and needs chemo -> single agent
Treatment – Metastatic, (cont’d)

- If HRP, HER2-neg, and stable -> anti-estrogen tx
  - Tamoxifen (pre or post menopausal)
  - Aromatase Inhibitor
    - With ovarian shut down in pre-menopausal
  - Choice of agents / sequence
    - Anastrazole = Letrozole
    - ?Exemestane different
    - Fulvestrant (Faslodex) intramuscularly
Treatment – Metastatic, (cont’d)

- If HRP, HER2-neg, and stable -> anti-estrogen tx
  - Choice of agents / sequence
  - **Combinations**
    - Letrozole + Palbociclib (Ibrance)
      - (CDK4 and CDK6 inhibitor)
    - Exemestane + Everolimus (Afinitor)
      - (mTOR inhibitor)
Treatment – Metastatic, (cont’d)

- If HRP, HER2-neg, and stable -> anti-estrogen tx
- If HER2-pos and needs chemo -> regimen containing anti-HER2 targeted therapy
- Dual anti-HER2 targeted therapy considered standard first line (if tolerated)
  - “THP” or “TCHP”
    - TCHP = Taxotere (Docetaxel) + Carboplatin + Herceptin (Trastuzumab) + Perjeta (Pertuzumab)
Treatment – Metastatic, (cont’d)

- “THP” or “TCHP” often followed by “maintenance” anti-HER2 therapy
  - Dual if tolerated
  - Single agent otherwise
- Continue indefinitely
  - So long as well tolerated
  - Remain efficacious
Treatment – Metastatic, (cont’d)

- Most common dose limiting side effects
  - Fatigue
  - (Myelosuppression from the chemo)
  - Cardio-toxicity
    - NOT coronary artery disease or MI
    - Rather pump function of heart (cardiomyopathy)
Cardiotoxicity

- Anthracyclines
  - Doxorubicin (Adriamycin)
  - Cardio-protectants (Zinecard)
- Anti-HER2 targeting (more reversible)
  - Trastuzumab (Herceptin)
  - Pertuzumab (Perjeta)
- (Synergistic cardiotoxicity NOT seen yet in combination)
Treatment – Metastatic HER2+

- First line
  - If also HRP then anti-estrogen therapy reasonable
  - If combination chemotherapy indicated then “THP or TCHP” (with anti-HER2 maintenance)
  - Multiple options after that
Treatment – Metastatic HER2+

- Second line
  - Ado-trastuzumab emtansine (Kadcyla)
    - Anti-HER2 directed conjugated to chemo
      (same risk of cardiotoxicity)
  - Lapatinib (Tykerb) + Capecitabine (Xeloda)
    - All oral (pills)
    - Crosses the blood brain barrier
    - Rash and diarrhea can be dose limiting
Treatment – Metastatic HER2+

- Third line
  - Whichever one not previously seen:
    - Ado-trastuzumab emtansine (Kadcyla)
    - Lapatinib (Tykerb) + Capecitabine (Xeloda)
  - Non-HER2 targeted therapy
    - (Same chemotherapy agents for NON-HER2 overexpressing patients)
    - Single agent, sequential therapy…
Summary

- Breast Cancer Histology, Pathology, Classification, Staining, and Sub-types
- Staging
- Clinical factors that impact decision making
Summary

- Treatment in the Adjuvant setting
  - Hormone Receptor Positive disease
  - HER2+ disease

- Treatment in the Metastatic setting
  - Hormone Receptor Positive disease
  - HER2+ disease