Neoadjuvant Therapy for Breast Cancer

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Objectives

• Discuss the role of neoadjuvant chemotherapy in breast cancer

• Discuss the different types of therapy utilized

• Discuss the side effects of therapy
Patient Case: JH

- 60-year-old lady with breast mass
- Diagnostic mammogram revealed a 24 mm x 12 mm oval density in the left breast middle depth
- Ultrasound demonstrated a 28 mm x 17 mm x 10 mm irregular mass in the left breast at 2:00
- Pathology demonstrated infiltrating ductal carcinoma, moderately differentiated
- Estrogen receptor was 100% positive, progesterone receptor was negative at less than 1%, Ki-67 was 50%, HER-2 by immunohistochemistry was 2+, and HER-2 by in situ hybridization was amplified.
- Breast MRI on March 10, 2016 which revealed a 2.4 cm x 1.9 cm mass in the left breast at 2:00 middle depth
Patient JH

• She was interested in lumpectomy
• No family history of breast cancer
• No other past medical history
• She is post menopausal
• Has strong supportive family and friends
Patient JH

• Is she an appropriate candidate for neoadjuvant chemotherapy?

• What factors are considered for chemotherapy?

• How should she be followed?
Neoadjuvant therapy

- Therapy prior to definitive surgical therapy
  - Chemotherapy
  - Endocrine Therapy
  - Biologic Therapy

- Objectives
  - Reduce the incidence of distant recurrence
  - Improve surgical outcomes
  - Early evaluation of the effectiveness of systemic therapy
  - Allows researchers the opportunity to obtain tumor specimens during preoperative treatment

- No mortality benefit (pre vs post surgery chemotherapy) for the most part
Chemotherapy

Tumor: Before

Chemotherapeutic agents attack cells that are rapidly dividing

Tumor: After
Endocrine Therapy
Biologic Therapy

Herceptin®
trastuzumab

PERJETA™
pertuzumab
Patient Selection

• Inoperable disease
  • Patients with locally advanced disease
    • Node positive tumors
    • Large breast tumors > 5 cm

• Operable disease
  • If breast conservation surgery is not possible
    • High tumor to breast ratio
    • Tumor Location
  • HER2 positive tumors
  • Triple Negative Tumors

• Medical contraindications to surgery upfront
HER2 positivity

NORMAL CELL
HER2 receptor

Normal amount of HER2
• Cells grow and divide normally

HER2-POSITIVE CANCER CELL
HER2 receptor

Too much HER2
• Cells grow and divide faster
Pretreatment Evaluation

• Histologic confirmation

• Receptor Status
  • ER
  • PR
  • HER2

• Breast MRI

• Staging evaluation to assess for distant disease
  • CT scans + Bone Scan
  • PET scan

• Confirmation of nodal status
  • Biopsy if node is palpable
  • Sentinel node biopsy can be considered

• Clip placement
Invasive ductal carcinoma

Invasive lobular carcinoma

http://www.health.harvard.edu/womens-health/breast-cancer
Breast magnetic resonance imaging - Figure 1

Figure 1. Before (left) and after (centre, right) introduction of gadolinium. Note the enhancement of both the tumor and neovascularity.

http://www.bcmj.org/article/breast-magnetic-resonance-imaging
PET Scan Cancer Left Breast

http://www.aboutcancer.com/breast_pet_scans.htm
HER2 positive

- Have a high rate of pathologic complete response (pCR)

- Chemotherapy + trastuzumab vs chemotherapy
  - Improved rate of pathologic complete response
  - Reduction in relapse rate
  - Trend towards lower mortality rate
  - Improvement in overall survival at 5 years

- Chemotherapy + trastuzumab + pertuzumab
  - Improved rates of pCR
  - No increase in toxicity
HER2 positive regimens

- Taxotere + carboplatin + trastuzumab + pertuzumab every 3 weeks x 6 cycles, followed by trastuzumab every 3 weeks to complete 1 year of therapy

- Adriamycin and cyclophosphamide every 2-3 week x 4 followed by weekly paclitaxel weekly x 12, pertuzumab every 3 weeks x 4, and trastuzumab every 3 weeks x 17 (1 year of therapy)

- There are other regimens as well. Chemotherapy is determined based on patient’s comorbid conditions, labs, cardiac evaluation, goals, etc.
Side effects of HER2 therapy

• Trastuzumab
  • fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia
  • Cardiac toxicity: Echocardiograms every 3 months
  • Infusion reactions
  • Pulmonary toxicity
  • Embryo-Fetal Toxicity

• Pertuzumab
  • Diarrhea, hair loss, low white blood cells, nausea, fatigue, rash, neuropathy
  • SIDE EFFECTS SEEN WHEN COMBINED WITH CHEMOTHERAPY and TRASTUZUMAB
Triple Negative

- Estrogen/Progesterone/HER2 negative

- Pathologic Complete Response (pCR) : 27-45% (compared to 10% with ER/PR positive and HER2 negative)

- Patients who achieve a complete pathologic response have a similar prognosis to patients with other breast cancer subtypes who achieve a pCR
Chemotherapy Agents Commonly Used

- AC – Doxorubicin (60 mg/m2) and cyclophosphamide (600 mg/m2) (AC) every two weeks (dose-dense) or three weeks for four cycles

- AC/taxane – AC followed by paclitaxel (175 mg/m2) every two or three weeks for four cycles or docetaxel (100 mg/m2) every three weeks for four cycles

- AC/weekly T – AC followed by weekly paclitaxel (80 mg/m2) for 12 weeks

- FEC – Fluorouracil (600 mg/m2), epirubicin (90 mg/m2), and cyclophosphamide (600 mg/m2) (FEC) every three weeks for four cycles

- FAC – Fluorouracil (600 mg/m2), doxorubicin (60 mg/m2), and cyclophosphamide (600 mg/m2) (FAC) every three weeks for four cycles

- TAC – Docetaxel (75 mg/m2), doxorubicin (50 mg/m2), and cyclophosphamide (500 mg/m2) for six cycles

- TC – Docetaxel (75 mg/m2) and cyclophosphamide (600 mg/m2) every three weeks for four to six cycles
Side effects of chemotherapy

- Hair loss, nausea, vomiting, diarrhea, constipation, mouth sores, neuropathy, electrolyte abnormalities, heart dysfunction, inflammation of the lungs, kidney failure, liver toxicity, rash, altered taste buds, infusion reactions, low red cells, low white cells, low platelets, skin changes, fatigue, nail bed changes
HER2 negative

• Post-menopausal women with ER/PR positive or negative
  • Chemotherapy is preferred over endocrine therapy (may allow breast conservation and make patients who are unresectable surgical candidates)

• Premenopausal women with ER/PR positive or negative
  • Chemotherapy better than endocrine therapy
  • If patient does not want chemotherapy, then consider initial surgery
  • Only offer endocrine therapy upfront to those who refuse surgery or chemotherapy
Endocrine Therapy

- Only for post menopausal women who are not candidates for surgery or chemotherapy unless under clinical trial

- Clinical Trial at Advocate Christ Hospital: Fulvestrant and/or Anastrozole in Treating Postmenopausal Patients With Stage II-III Breast Cancer Undergoing Surgery

- Small amount of evidence comparing to chemotherapy (study of 239 women)
  - No difference in response rates
  - Similar time to clinical response

- Choice of Endocrine therapy
  - Aromatase inhibitors better than tamoxifen
    - Higher response rates
    - Higher rate of breast conserving therapy

- Duration of therapy: 3-4 months, maybe longer based on response
Side Effects of Endocrine Therapy

- Tamoxifen
  - hot flashes, vaginal dryness, low libido, mood swings, and nausea
  - Uterine cancer risk
  - Deep vein thrombosis
  - Hair loss(< 9%)
  - Cataracts
  - Interaction with anti-depressants except Venlaxafine (Effexor) (the others lower the active metabolite of tamoxifen)

- Aromastase Inhibitors (anastrozole, exemestane, letrozole)
  - Bone density loss
  - Increase in cholesterol
  - hot flashes, night sweats, and vaginal dryness
  - Joint aches
  - Joint stiffness

- COMPLIANCE IS VERY IMPORTANT FOR ESTROGEN RECEPTOR BREAST CANCER
Treatment Evaluation During Therapy

• Clinical examination
  • every 2-4 weeks for patients on chemotherapy
  • Every 4-8 weeks for patients on endocrine therapy

• Imaging only if disease progression is suspected

• No role for repeat biopsy outside of a clinical trial
Gene Expression Profiling

- **Oncotype Dx**: Recurrence assay, 5 reference genes, 16 genes associated with cancer recurrence
  - Typically used in the adjuvant setting
  - ER positive, PR positive or negative, and HER2 negative
  - Majority of data are in the adjuvant setting

- In an Italian Study, the Oncotype Dx was a strong predictor of pCR in women with locally advanced disease receiving neoadjuvant chemotherapy
Post Therapy

• Progressive Disease during therapy → MASTECTOMY

• Partial response, lumpectomy not possible → MASTECTOMY

• Partial response, lumpectomy possible → LUMPECTOMY

• Complete Response → LUMPECTOMY
Patient JH

• Started chemotherapy with carboplatin, docetaxel, trastuzumab, and pertuzumab given the HER2 positive disease x 6 cycles

• Her echocardiogram was followed every 3 months (no cardiac toxicity)

• MRI breast after neoadjuvant therapy revealed a complete response to chemotherapy with interval resolution of the mass.

• Underwent lumpectomy: Pathology revealed no evidence of carcinoma with 3 negative nodes. She had a complete pathologic response to chemotherapy.

• She will now receive radiation therapy and then endocrine therapy