Adjuvant Systemic Therapy in Early Stage Breast Cancer

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Treatment of Early Stage Breast Cancer (Adjuvant Therapy)

• Breast cancer is most curable when detected early
  – Micrometastases (undetectable) can exist at time of diagnosis in many patients, leading to eventual recurrence

• Multidisciplinary care is critical for best outcomes
  – Surgery
  – Radiation therapy
  – Adjuvant systemic (drug) therapy reduces risk of recurrence and death
    » Should be tailored to the patient and tumor
Is Screening or Adjuvant Systemic Therapy More Important in Breast Cancer Survival?

U.S. Breast Cancer Death Rates

Both matter!

Berry D et al, NEJM 353: 1784-1792, 2005
Systemic Therapy for Early Stage Breast Cancer

- Endocrine therapy
- Chemotherapy
- Targeted Therapies
Endocrine Therapy in Breast Cancer

Aromatase inhibitors (anastrozole, letrozole, exemestane), ovarian suppression (leuprolide, goserelin)

SERMS (tamoxifen, toremifene), SERDS (fulvestrant)

Estrogen

Estrogen Receptor

Cell Growth and Division
WHO Model List of Essential Medicines

Antineoplastic drugs relevant to breast cancer

• Endocrine therapy:
  – Tamoxifen
  – Anastrozole (Arimidex)
  – Leuprolide (Lupron)

Early Breast Cancer Trialists’ Collaborative Group
Clinical Trials of Tamoxifen in Early Stage Breast Cancer: Disease-free Survival

ER Negative

Adjuvant tamoxifen doesn’t impact recurrence in ER negative breast cancer

Tamoxifen effective in both pre- and postmenopausal women

ER Positive

Adjuvant tamoxifen significantly reduces recurrence in ER positive breast cancer

tamoxifen
control
Aromatase Inhibitors versus Tamoxifen in Early Breast Cancer: Meta-analysis of the Randomised Trials
EBCTCG Lancet 386:1341-52, 2015

Under study: Extended duration Aromatase Inhibitors (up to 10 years)
Adjuvant Endocrine Therapy in Early Stage Breast Cancer

- **Tamoxifen**: substantial clinical efficacy, low cost, and several decades of use throughout world
  - Still the standard for premenopausal women
  - Reasonable for many postmenopausal women
  - Longer duration (> 5 years) may benefit some patients

- **Aromatase inhibitors**: additional small reduction in breast cancer recurrences (and deaths) compared to tamoxifen
  - Only effective in postmenopausal women
  - Side effects different (?better)

- **Ovarian suppression**
  - Only effective in premenopausal women
  - Addition to tamoxifen (or aromatase inhibitors) may add benefit in subset of young women (< age 35)
Chemotherapy for Early Stage Breast Cancer

- **THE PAST** (2000 NCI Consensus Development Conference on Adjuvant Breast Cancer)
  - *Chemotherapy should be offered to the majority of women with early stage breast cancer regardless of size, lymph node, menopausal or hormone receptor status*

- **THE PRESENT AND FUTURE**
  - Individualizing estimates of recurrence risk and chemotherapy benefit using genomic/molecular profiling
    - *Many patients don’t need chemotherapy*
Genomic Profiling in Early Stage Cancer
Oncotype Dx 21-Gene Recurrence Score Assay

Developed to help define which “low risk” ER+, lymph node negative patients do not need chemotherapy, and which may benefit.
Genomic Profiling in Early Stage Breast Cancer: 21-Gene Recurrence Score Assay

Recurrence Score in LN-, ER+ if given only 5 Years Tamoxifen

**Lower RS**
- Less likelihood of recurrence
- Greater tamoxifen benefit
- Minimal chemotherapy benefit

**Higher RS**
- Greater likelihood of recurrence
- Less tamoxifen benefit
- Clear chemotherapy benefit
Chemotherapy Dose Matters

Adjuvant Chemotherapy - 20 Year Follow-up Milan Study


Giving < 85% of full dose is the same as no chemo

If chemotherapy is given, it should be given at full dose
WHO Model List of Essential Medicines

Antineoplastic drugs relevant to breast cancer

- Chemotherapy:
  - Doxorubicin (Adriamycin)
  - Cyclophosphamide (Cytoxan)
  - Paclitaxel (Taxol)
  - Docetaxel (Taxotere)
  - Fluorouracil (5-FU)
  - Methotrexate

- Chemotherapy (cont):
  - Carboplatin
  - Gemcitabine (Gemzar)
  - Capecitabine (Xeloda)
  - Vinorelbine (Navelbine)

Adjuvant Chemotherapy in Early Stage Breast Cancer

- Adjuvant chemotherapy reduces recurrences and deaths
  - Reducing dose from that proven to be effective in clinical trials reduces benefit
  - Chemotherapy drugs have significant side effects

- For unselected patients/tumors:
  - Anthracyclines (doxorubicin, epirubicin) better than CMF regimens
  - Taxanes (paclitaxel, docetaxel) add to anthracyclines

- Not all patients/tumors benefit from chemotherapy!
  - ER-negative, high grade, and HER-2+ tumors get most benefit from chemotherapy
Four US FDA-Approved Drugs with HER2 as a Target

- Pertuzumab: Anti-HER-2 Antibody
- Trastuzumab: Anti-HER-2 Antibody
- Lapatinib: Dual HER-1/HER-2 Tyrosine Kinase Inhibitor
- Ado-trastuzumab emtansine: Antibody-Drug Conjugate

HER-2

cancer cell

nucleus

cell division
Adjuvant Trastuzumab: Combined Analysis of NSABP B-31 and N9831


- Risk of breast cancer recurrence reduced by 52% at 3 yrs
- Risk of death decreased by 33% at 2 yrs

Antineoplastic drugs relevant to breast cancer

• Targeted Therapy
  – Trastuzumab (Herceptin)

ASCO Guideline: HER2 Targeted Therapy for Early Stage Breast Cancer

Giordono S et al, J Clin Oncol 2014

• Anti-HER2 monoclonal antibody trastuzumab for 1 year is standard
  – Reduces recurrence by 1/2 & deaths by 1/3 when added to chemo in early stage breast cancer

• All regimens include chemotherapy in addition to HER2-targeted therapy
Systemic Treatment of Early Stage Breast Cancer: Summary

• Main principles of modern oncology
  – Multidisciplinary treatment
  – Evidence-based medicine
  – Individualized (tailored) therapy

• Primary goals of therapy
  – Adjuvant: curative intent