Breast Cancer Review

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Breast Cancer in the US

- Leading Ca dx in women, second in deaths
- Race: white > AA incidence
  - Higher stage at dx (AA)
  - Higher death rate (AA)
- Risk factors
  - Nulliparity
  - First child after 30
  - Early menarche, late menopause
  - Age
  - Post meno obesity

Breast CA in the US

- Risk factors (cont)
  - Alcohol intake
  - Decreased physical activity
  - Family hx
  - ADH, LCIS, DCIS
  - Multiple bxs
  - RT (Hodgkins)

Breast Ca in the US

- Genetic Risk
  - BRCA 1, 2
    - 5-10 % of all breast CA
    - Ashkenazi Jewish heritage is over-represented
    - Generally young (<50) and multiple relatives
    - Breast/Ovary/Male Breast Ca
  - Extended Genetic evaluation
    - Li Fraumeni (P53 tumor suppressor gene) e.g.

Risk Reduction: Chemoprevention

- Tamoxifen (NSABP P1 trial)
  - Tam vs Placebo in pre/post meno Pts at risk
  - 49% reduction in Invasive Dz with Tam
- Tamoxifen/Raloxifene (NSABP P2 Trial “STAR”)
  - Only post meno Pts at risk
  - Equal benefit in reducing invasive dz
  - Decreased non invasive events (DCIS) with Tam
- Downside?
  - No OS impact, side effects

Genetic Risk Reduction: Surgery

- Bilateral Mastectomy
  - 90% lifetime reduction
- Bilateral Salpingo-Oophorectomy
  - 95% lifetime reduction of Ovarian CA
  - 50% reduction in hormone sensitive Breast CA in pre-menopausal women

Alternatives? Breast: B/L mammo and MRI

Ovary: none

Carcinoma in situ

- Lobular Ca in situ (LCIS)
  - Risk factor not a precursor
  - No tx, B/L Mast or Tamoxifen
- Ductal Ca in situ (DCIS)
  - Precursor lesion (Stage 0)
  - Formerly known as Intraductal Carcinoma
  - Lumpectomy/RT, Mastectomy
  - +/- Tamoxifen if ER+

Invasive Breast Cancer

- TNM staging: Stage I-IV
- Local treatment
  - Lump/SLN $\longrightarrow$ RT, Mastectomy
  - SLN: radioactive blue dye, diminishes risk of edema
  - RT: brachytherapy vs whole breast
  - Equivalent OS, dissimilar local RR
  - RT after Mast
    - 5 cm +
    - 4 + LNS
    - Pos margins, IBC,

Why do Adjuvant Treatment?

- Early randomized studies with active agents vs placebo demonstrate survival superiority
- Only explanation of benefit is microscopic disease at dx
- Works equally well neoadjuvantly vs adjuvantly
  - Breast conservation
  - Locally advanced disease
- "Magic" numbers: 6 and 15
  - 6 cycles or more to achieve 99.9 log kill in culture
  - 15% or better defines an active agent at NCI
- General rule of thumb in any disease: find active agents in Metastatic disease, then move them up and combine them

Who do we treat?

- The ones most at risk…who are they? How do we determine risk?
- Adjuvant treatment is best thought of as relative risk reduction :
  - 25% RRR with hormones alone
  - 33% RRR with chemo alone
  - 50% RRR with chemo/herceptin
- TNM
- ER/PR
- Her 2 neu
- Molecular testing

Tools to help decide Who & What

- Adjuvant Online
  - Age, TNM, ER, Grade, and Comorbidities
  - Gives estimate of survival vs death from Breast CA vs other causes
  - Allows for hormones if approp. and different generations of chemo
  - Neg: no input for Her 2 neu
- Oncotype DX
  - 21 markers tested by RT-PCR in paraffin
  - Validated by retrospective data from NSABP trials with Tam and CMF
  - Score (Low, Intermed, High)
  - Recurrence risk for distant disease
  - Focused on LN negative, hormone positive disease at least 5 mm

Adjuvant Hormonal Therapy

- Additional benefit seen in every trial in pre and post menopausal pts with ER or PR positivity
- Tamoxifen (competes with Estrogen for receptor)
  - Pre and Post
- Aromatase Inhibitors (Decreased Est production)
  - Post only
- Ovarian Suppression
  - Infrequent approach but alternative to Tam
  - Pre only

Other Hormonal Adjuvant Data

- Multiple "switching trials" all positive
- Tam 5 yrs ⟶ Letrozole
- Tam 5 yrs versus 10 yrs (Atlas trial)
- Tamoxifen
  - Hot flashes, emotional lability, vag dryness
  - Thromboembolic events, cataracts, Uterine CA
- AIs
  - Arthralgias/myalgias, hot flashes, GI upset
  - Accelerated bone loss

Adjuvant Chemotherapy Principles

- Short programs (3 mos v 5-6 months)
- Anthracyclines (Adriamycin, Epirubicin)
  - Alopecia, myelosuppression, mucositis
  - Vesicants, myocardium at risk
- Taxanes (Paclitaxel, Docetaxel)
  - Alopecia, myelosuppression, neuropathy
- Trastuzamab (Herceptin)
  - Humanized monoclonal ab to Her 2 neu
  - Infusion rxns, nausea, CHF

Locally Advanced and IBC

- Locally Advanced
  - Neglected or aggressive biology
- Inflammatory Breast CA (IBC)
  - Diffuse erythema, induration and peau d'orange
  - Dermal lymphatic invasion on bx
- Neoadjuvant Chemotherapy → Mastectomy → Radiation → Hormones ?/Herceptin?
- Both entities have cure rates albeit low at 30% for IBC and perhaps higher with locally advanced

Metastatic Breast Cancer

- Generally considered incurable
- OS 2 yrs per MKSAP, subsets much longer
- Local tx goals: palliation and perhaps better survival in some papers
- Rule of thumb: Bx first recurrence
  - Different Cancer?
  - Different biological features?
- Bone/soft tissue presentation and ER/PR+? Hormone
- Threatening, organ involvement? Sequential chemo +/- Herceptin and analogues

Metastatic Breast CA (cont)

- Bone Metastases
  - Bone only, best survivors of all
  - Bone preservation
    - Bisphosphonates (Pamidronate, Zoledronic Acid)
      - AKI, nausea, bone pain, ONJ, hypocalcemia
    - Rank Ligand Inhibitor (Denosunab)
      - Increased infection risk, nausea, bone pain, ONJ, hypocalcemia

Breast Cancer Followup

- Monthly SBE
- Q 6-12 month breast imaging: mammo, US, +/- MRI
- Q 3 mos, 4 mos, 6 mos, yearly exams
- **Routine studies (labs and imaging) in otherwise asymptomatic patients have not been validated to alter survival (dexascan excluded)**
- Reduction in fat intake and weight are helpful
- Vit D and Calcium supplementation
- Vag estrogens are safe (Vagifem, Estring)
- Avoid any systemic estrogens

Breast Cancer Followup (cont)

- Venlafaxine has been proven to reduce vasomotor sx by 67%
- Beware of interaction of antidepressants that inhibit CYP2D6 pathway in liver. They interfere with TAM metabolism
  - Bupropion (Wellbutrin)
  - Fluoxetine (Prozac)
  - Paroxetine (Paxil)
  - (Citalopram, Celexa) weak
- Ovarian dysfunction can last up to 18 mos!