ADJUVANT SYSTEMIC TREATMENT FOR BREAST CANCER
1960 - 2018

ADJUVANT TREATMENT

- Definition – traditionally treatment administered following primary cancer treatment
- Breast cancer – primary treatment is surgery
- Adjuvant systemic treatment includes
  - Chemotherapy
  - Anti-hormonal therapy
  - Monoclonal antibody therapy
  - Bisphosphonates

**Radiotherapy is also considered adjuvant but not systemic
- although systemic impact

Adjuvant therapy for breast cancer prior to 1977

- Treatment was surgery
- Most common operation was a radical mastectomy

Chemotherapy

- History of development of effective chemo agents
- Use of single agents vs multiple agents
- Adjuvant chemo vs neoadjuvant chemo
The first rule of therapeutics

Primum non nocere
- Hippocrates

History of Chemo-alkylators

- 1890’s – synthesis of alkylating agent Nitrogen Mustard
  Term “mustard” comes from the pungent smell (not the mustard plant)
- Early 1900’s – discovery of vesicant properties of Nitrogen Mustard
- WW1 – mustard gas (a volatile form of nitrogen mustard) used in war
- 1943 – US Liberty ship John Harvey (carried mustard gas) was hit during an air raid on Berlin. Profound bone marrow and lymphoid aplasia was noted in survivors.
- 1946 – Goodmann and Gilman – striking temporary dissolution of lymphoid tumor masses in murine models
- 1950’s – most research was military
- 1963 – resumed human testing demonstrating activity vs lymphoid tumors and epithelial cancers
- 1963-present – further development of family of chemo agents known as Alkylators

Alkylators used in breast cancer

Historically - melphalan
Currently - cyclophosphamide

History of chemotherapy - antimetabolites

- 1940’s – studies demonstrated that addition of folic acid worsened leukemia and diet deficient in folic acid produced improvement in the Rx of ALL
- 1947 – Sidney Farber used an inactive analogue of folic acid, amethopterin, to induce remission in children with ALL (blocking availability of folic acid for leukemic cells)
- 1950 – another analogue, amethopterin (less toxic than aminopterin), was proposed for treatment of leukemia. This was first effective anti-metabolite known by trade name Methotrexate.
- 1956 – Methotrexate was the first curative drug treatment for a solid tumor, choriocarcinoma (malignant trophoblastic cancer usually of the placenta)
- 1956 – present – development of 2nd major family of chemo agents known as Anti-metabolites
Anti-metabolites used in breast cancer

- Methotrexate
- 5-fluorouracil

Methotrexate (MTX, Folex)

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5-Fluorouracil (5-FU) (pyrimidine analogue)

Uracil

5-Fluorouracil

Thymidylate synthetase

Its analogue is 5F-dUMP

History of Chemotherapy - anticancer antibiotics

- 1950’s Farmitalia (Italian pharmaceutical company) – organized effort to find anticancer compounds from soil-based microbes
- Streptomyces peucetius – produced antibiotic with activity against murine tumors. Also produced red dye
- French researchers found similar agent at same time
- Both Italians and French wanted to name drug. Compromise: Daun (pre Roman tribe that occupied area of Italy where compound found) and French word for ruby, Rubis(red) combined and drug named daunorubicin
- 2nd and possibly most important member of the family of Naturally Occurring Agents
History of Chemotherapy
-naturally occurring agents
• Cantharanthus roseus (Madagascar periwinkle) – a plant used in folk remedies for centuries eg. diabetes
• 1950’s – a number of alkaloids identified
• 1950 – 1960 – trials done in diabetes very disappointing but anti-proliferative actions noted
• 1963 – J.D. Armstrong identified Vincristine and marketed by Eli Lily (a major player in early diabetes research)
• 1963-present – 4 major analogues identified including Vinblastine, Vindesine, Vinorelbine, and Vinflunine
• 1st plant alkaloid of 3rd major family of chemo drugs, the Naturally Occurring Compounds
** alkali (Latin) from alqalwi (Arabic) for ashes of plants and oid from Greek (like)

Chemotherapy for breast cancer 1965
• 3 families of chemotherapy agents available
  - Alkylators
  - Anti-metabolites
  - Naturally occurring agents
• How to use them ?
  - Really uncertain

But we had some ideas !!!
• Lymphomas responded well to single agent chemo but no cures
• 1966 - Combination chemotherapy cured Hodgkins Disease (sense that correct combination could cure all cancers)
• Late 1960’s single agent chemo shown to shrink metastatic breast cancer lesions
Where did we proceed?

- Patients with lymph node positive breast cancer in 1970 died more than 60% of the time within 5-10 years despite radical surgery
  - comparable patients now present earlier

Early attempt at adjuvant chemo

- Single agent Melphalan (an alkylator) was given after radical surgery
  - First adjuvant chemotherapy trial for breast cancer
  - No improvement in survival
  - Similar to results of single agent therapy for lymphoma

So where from there?

- Bonnadonna 1977 combined 3 drugs given after surgery
  - Cyclophosphamide
  - Methotrexate
  - 5-Flourouracil

Adjuvant CMF

- Survival rates at 5 years increased
  - from 40% to 60%

- The original cohort of patients treated with CMF still have a survival advantage over the control group
Adjuvant CMF

- Became standard of care post surgery for lymph node positive breast cancer

CMF

- Cyclophosphamide – 20 to 30% RR when used alone in the metastatic setting
- Methotrexate – 20 to 30% RR
- 5-FU – 20 to 30% RR
- What if we used more active agents?

Naturally occurring agents

- Anthracyclines – 50% RR
- Taxanes – 50% RR

Addition of more active agents

- Addition of an anthracycline to CMF decreased annual risk of death by 11% vs CMF alone (Milan)
- Addition of docetaxel to anthracycline regimens increased relapse free survival from 68% to 75% (NEJM June 2, 2005)

Neoadjuvant Chemotherapy

- Chemotherapy given before definitive therapy (surgery)
  - Downstages tumor
  - Optimizes surgical outcomes
  - Reduces risk of breast cancer recurrence
  - probably minimal impact on survival
  - in vivo assessment of chemo responsiveness

What about stage 1 breast cancer?

- Outcomes also improved with best combination chemo
- Magnitude of benefit not as impressive as stage 2
- Toxicity including long term toxicity is the same
What about stage 1 breast cancer?

- Should all stage 1 breast cancer patients receive chemotherapy?
  - Adjuvant on line
  - NHS predictive tool
  - Oncotype Dx

NHS predict

- 40 yo woman
- Screen detected cancer
- 22 mm
- Grade 3
- 0 lymph nodes
- ER positive
- Her-2/neu negative

Results – 100 patients

- 93% alive with no adjuvant Rx at 5 years, 81% at 10 year
  - 2 extra alive at 5 years due to anti-hormone Rx
  - 5 extra at 10 years
  
  - 3 extra alive with anti-hormone Rx and chemo
  - 9 extra at 10 years

How do we pick out who might benefit – Oncotype Dx

Standard adjuvant chemotherapy for stage 2 and high risk stage 1 breast cancer

FEC-100
- 5-fluorouracil
- Epirubicin
- Cyclophosphamide

Docetaxel

Side effects of FEC-D

- Hair loss
- Nausea and vomiting
- Sepsis
- Cardiomyopathy
- Second malignancies
- “Hurts all over”
- Neuropathy
- Brittle nails
Adjuvant anti-hormonal therapy for breast cancer

- History of drug development
- Available agents
- Toxicity of anti-hormonal agents

History of anti-hormonal therapy - for breast cancer

- 1906 - oophorectomy could result in regression of skin metastases in breast cancer (Beatson)
- 1900's - adrenalectomy could result in secondary responses
- Mid 1900's - hypophysectomy could result in occasional responses
- 1960's - acceleration of BCP research led to development of morning after pill
  - Tamoxifen: relatively ineffective
  - Blocked estrogen receptor in breast not endometrium
  - Effective in treatment of breast cancer mets
  - Sleeping pill Doriden (glutethimide) associated with adrenal suppression
    - Modified to reduce sedation (aminogluthimide)
    - Used in Rtx of metastatic breast cancer
    - Not effective though lost aromatase (estrogen synthetase) inhibitor
      - Effective in postmenopausal patients of aromatase inhibitors (aromatase and testosterone to estradiol)
Historical - Today

- Oophorectomy - tamoxifen
- Adrenalectomy - estrogen synthesis inhibitors (aromatase inhibitors)
- Hypophysectomy - LHRH inhibitors (LH releasing hormone agonists)

Can anti-hormonal agents improve outcomes after breast cancer surgery

- A few clues
  - Patients treated with CMF did better if menopause induced
  - Breast cancer essentially never seen prior to menarche

Early Breast Cancer Trialists' Collaborative Group (Overview)

- Lancet 1992
  - Adjuvant value of oophorectomy in pre menopausal women demonstrated

OVERVIEW

- Women less than 50
  - Adjuvant tamoxifen with chemo vs chemo alone
    - Increased survival by 23%

Overview

- Women older than 50
  - Increased survival by 20%
    - independent of chemo

Overview

- Overall in Estrogen Receptor expressing breast cancer
  - Tamoxifen vs no tamoxifen increased survival by 21% at 5 years
NIH guidelines following the Overview - 1994

* any women with any size invasive breast cancer with any expression of estrogen receptor should be offered anti-hormonal therapy *

Adjuvant tamoxifen

• Impact is greater with :
  - Severity of disease (stage 2 greater than stage 1)
  - Correlation between degree of ER expression and benefit
  - Probably more impactful in post menopausal setting than pre menopause

Is 5 years Rx Best ?

• ATLAS trial
  - 12,894 patients after 5 years Tamoxifen
  - Either placebo or 5 more years Tamoxifen
    • Results
      - Decreased recurrences
        - 711 vs 617 (p=0.002)
      - Decreased all cause mortality
        - 722 vs 639 (p= 0.01)

Toxicity of Tamoxifen

• Increased thromboembolic disease
• Increased incidence of endometrial carcinoma
Are aromatase inhibitors as active as tamoxifen in post menopausal women

- Equal or slightly better

ATAC trial

- Anastrozole, Tamoxifen, Alone, or Combined
- Results
  - Anastrozole superior in:
    - Disease free survival (HR=.86)
    - Time to relapse (HR=.79)
    - Time to distant relapse (HR=.85)
  - Combination inferior

Limitation of Aromatase Inhibitors

- Can only be used in post-menopause

AI’s use premenopausally

- Decreases estrogen production by ovary
- Increases LH, FSH release by pituitary
- Increases attempt at estrogen production by ovary i.e. hyperstimulation
- Leads to development of cystic ovaries and ultimately does not stop ovarian estrogen production
- Actually due this hyperstimulation, can be used to induce ovulation

Induction of Menopause

- Oophorectomy
- Pituitary inhibition
- Chemotherapy
Side effects of aromatase inhibitors

- Hot flashes
- Aches and pains
- Osteoporosis

Role of monoclonal antibodies in adjuvant treatment of breast cancer

- Agents include:
  - Trastuzumab
  - Bevacizumab
  - PD-1 and PD-L1 inhibitors

Monoclonal antibodies

Mechanism of action:

1. make cancer cell more visible to the immune system
2. block growth signals
   - target is EGFR
3. stop new blood vessels from forming
   - target is VEGF

Monoclonal Antibody History
MOAB’s to HER domain of EGFR

• Trastuzumab, Pertuzumab

• Up to 30% of breast cancer overexpress HER2 gene product (probably less in NS)

• Overexpressed HER-2/neu can lead to acceleration of tumor growth

MOAB’s to HER domain of EGFR

• Blocking HER increases both response rate and survival in metastatic breast cancer

• Increases “cure” in early stage HER positive breast cancer (adjuvant)

Evidence for role of Herceptin adjuvantly
- British meta-analysis

• Increases cure rate in “curable” breast cancer by 11%
  \( HR = 0.66 \)

• Increases DFS in “incurable” breast cancer
  \( HR = 0.6 \)

Toxicity of Herceptin

• Decreases LV ejection fraction
  \( RR = 1.83 \)

• Usually reversible

NEJM October, 2011
- D. Slamon et al

• HER 2-targeted Rx recommended for HER 2 positive patients with or without lymph node involvement

• Best to give adjuvant HER 2-targeted Rx as early as possible but late Rx also effective (HERA trial)
Adjuvant bisphosphonate Rx

- ASCO guidelines
  - With high risk patients receiving adjuvant chemo, addition of zolendronic acid 4 mg IV q6 months x 3-5 years improved outcomes by approx. 2.6 %  
  - RR = .82
- Rationale:
  - Decreases bony mets
  - Decreases EGFR activity

Impact of adjuvant systemic Rx

- Prior to mid-70’s
- 39 yo
- Breast cancer detected by patient
  - 7 cm breast tumor
  - Grade 3
  - ER positive
  - 2-3 positive lymph nodes
  - Her-2/neu positive

**** 5-year survival with rad.surgery = 40% (NHS predict)

Impact of adjuvant treatment 2018

- Same features
- Treated with
  - Chemotherapy
  - Anti-hormonal therapy
  - Monoclonal antibody vs Her-2/neu
  - Bisphosphonate Rx

- 5-year survival = 80% (NHS predict)

Adjuvant on line prediction

- No Rx
  - Chance of death from breast cancer in first 10 years = 57.7 %
  - Chance of death from breast cancer with all modalities of treatment = 23.3 %
Future of adjuvant therapy for Breast cancer

- Improving predictors of benefit
- Improving treatment
  - Cyclin dependent kinase inhibitors
  - Immunotherapy