CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM

Breast Cancer Educational Program

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Adjuvant Systemic Therapy For Early Breast Cancer:

Who, What and for How Long?

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Disclosures

- Advisory Board Member: Roche, Novartis and Bristol Myers Squibb

Mitigating Potential Bias

- No bias in this talk as this is an overview of treatment options based on the published data and according to local, national and international guidelines

Learning Objectives

1. Explain the indications for adjuvant systemic therapy for women with early breast cancer

2. Describe the common adjuvant chemotherapy regimens

3. Name the adjuvant endocrine therapy options for:
   - premenopausal and perimenopausal women
   - postmenopausal women

Overview

- Goals of adjuvant systemic therapy
- Adjuvant chemotherapy
- Adjuvant endocrine therapy
- Her2 + early breast cancer

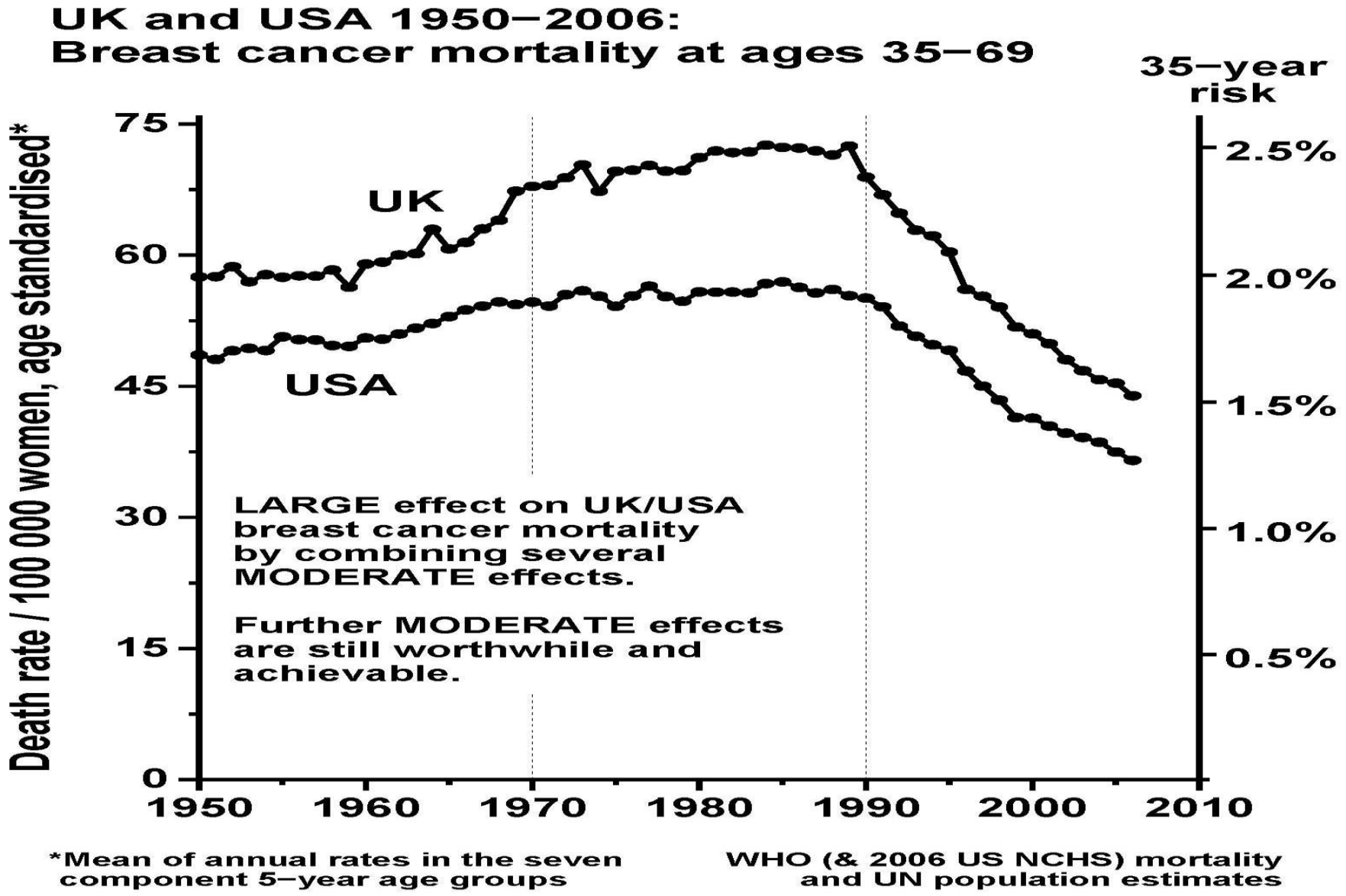
Ms. MK

- 40 year old previously healthy premenopausal female and now diagnosed with a Stage IIA (T1c N1 M0) right breast cancer after mastectomy and axillary node dissection in March 2014.
- Pathology showed a 1.7 cm invasive ductal cancer, poorly differentiated at grade III (6/9). There was no lymphovascular invasion and margins were negative.

  ER is 7/8 and PR 6/8 and Her-2 is negative. Three of eight axillary nodes involved (3/8)
- She is referred for discussion of adjuvant systemic therapy

Canadian Breast Cancer 2015 Statistics

- The most common cancer in women and the 2nd leading cause of death
- Estimate that 25,000 women will be diagnosed with breast cancer in 2015
- 5000 women will die of the disease
- In Manitoba, ~800 new cases and 210 deaths


UK and USA 1950–2006:
Breast cancer mortality at ages 35–69
35–year risk
Death rate / 100 000 women, age standardised*
75
60
45
30
15
0
2.5%
2.0%
1.5%
1.0%
0.5%
UK
USA
LARGE effect on UK/USA breast cancer mortality by combining several MODERATE effects.
Further MODERATE effects are still worthwhile and achievable.
1950
1960
1970
1980
1990
2000
2010
*Mean of annual rates in the seven component 5–year age groups
WHO (& 2006 US NCHS) mortality and UN population estimates

Adjuvant systemic treatment of early breast cancer is the treatment of microscopic metastatic deposits

Goals of Adjuvant Therapy for Cancer:

1) Increase survival
2) Reduce recurrence
3) Minimize adverse effects

Adjuvant Systemic Therapies

- Chemotherapy
- Endocrine therapy
- Other targeted therapies (anti-Her 2)

Adjuvant Chemotherapy

Development of Adjuvant Chemotherapy for Breast Cancer

- **Before anthracyclines**
  - CMF, CMFVP
- **Anthracyclines**
  - Combinations: AC, FAC, AVCMF, FEC, CEF
- **Taxanes (Paclitaxel/Docetaxel)**
  - Sequential: A⇒ T⇒ C or AC⇒ T
  - Combinations: AT, TAC
- **Biologic Modifiers: Trastuzumab**
  - Integration in chemotherapy strategies

EBCTCG Meta-analysis of all adjuvant trials

Lancet 2012

- Most recent meta-analysis of outcomes in 100,000 women with early breast cancer in > 100 trials of adjuvant chemotherapy
- Polychemotherapy continues to reduce breast cancer mortality by ~ one third, independent of age (up to at least 70 years) or ER status

Who needs adjuvant chemotherapy?

Decision to give adjuvant therapy based on:

- Individual risk of recurrence
- Absolute benefit of therapy
- Side-effects of treatment
- Other co-morbidities
- Patient preference

Traditionally, classic clinicopathological features are used to determine clinical outcome in breast cancer

Common prognostic, predictive and clinical factors in breast cancer

- axillary lymph node status (N stage)
- tumour size (T stage)
- histologic grade
- presence of lymphovascular invasion (LVI)
- hormone receptor expression
- Her-2 status
- Age < 35

Estimating risks of breast cancer recurrence

- Computerized modelling

  eg. Adjuvant! Online

- Genomic analysis of tumors

  eg. Oncotype DX assay

Adjuvant! Online

Decision making tools for health care professionals

Adjuvant! for Breast Cancer (Version 8.0)

Patient Information

Age:	070
Comorbidity:	Minor Problems
ER Status:	Negative
Tumor Grade:	Grade 3
Tumor Size:	2.1 - 3.0 cm
Positive Nodes:	1 - 3
Calculate For:	Relapse
10 Year Risk:	62 Prognostic

Adjuvant Therapy Effectiveness

Horm:	Tamoxifen (Overview 2000)
Chemo:	CMF-Like (Overview 2000)
Hormonal Therapy:	0
Chemotherapy:	23
Combined Therapy:	23

No additional therapy:

30.2 alive and without cancer in 10 years.

58.7 relapse.

11.1 die of other causes.

With hormonal therapy: Benefit = 0.0 without relapse.

With chemotherapy: Benefit = 7.9 without relapse.

With combined therapy: Benefit = 7.9 without relapse.

Print Results PDF | Access Help and Clinical Evidence

Images for Consultations

Oncotype DX Assay

- In newly diagnosed pts with LN- and ER+ and Her2- breast cancer, the Oncotype DX assay can be used to predict the risk of cancer recurrence (RS) in pts treated with tamoxifen
- Can also be used to identify patients predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and who may not require chemotherapy
- Patients with high RS may achieve more benefit from chemotherapy than tamoxifen only
- This assay is not currently funded in Manitoba (>$4000 USD)
- Cannot endorse yet for treatment-decision making in LN positive breast cancer and current NCIC MAC.15 trial is exploring use of Oncotype DX in women with ER + and Her-2 negative breast cancers involving 1-3 positive LNs

Risk Groups

- "Low risk": LN negative, ≤ 2 cm, grade I histology and no other adverse prognostic factors or Oncotype DX Recurrence score < 18
- "Intermediate risk": all other combinations of factors that do not fit into either the low or high risk criteria or Oncotype DX Recurrence score 18-30

“High Risk”

- positive axillary lymph nodes ***or***
- negative lymph nodes, tumour >1 cm and *one* adverse prognostic factor:
    - ER/PR negative
    - Her2 positive
    - Grade 3 histology
    - Presence of lymphovascular invasion
    - Tumour > 3 cm
    - Oncotype DX recurrence score >30

What chemotherapy?

Common adjuvant chemotherapy regimens

- 1st generation: eg. CMFx6, ACx4, FEC-50x6
- 2nd generation: superior to 1st generation regimens by reducing risk of death or recurrence by an additional relative 15-20%

  eg. FEC-100x6, CAFx6, CEFx6, ACx4→Px4, TCx4
- 3rd generation: relative 15-20% better than 2nd generation regimens and a relative 35% better than 1st generation regimens

  eg. FEC-D, TAC, dd AC→ dd P, AC x 4 followed by weekly P, dd EC followed by P

★ regimens used locally

Preferred chemotherapy regimens:

- Low risk: nil or endocrine therapy alone
- Intermediate risk: consider 2nd generation chemotherapy regimen eg TC
- High risk: 3rd generation regimen eg FECD

Adjuvant chemotherapy: for how long?

Duration of adjuvant chemotherapy

- Usually 4-6 cycles but depends on the specific regimen

- For patients receiving neoadjuvant chemotherapy (usually stage III tumours)

  - use 6-8 cycles of chemotherapy but there is no evidence that 8 cycles is superior to 6 cycles

……Back to Ms. MK

- 40 year old previously healthy premenopausal female and now diagnosed with a Stage IIA (T1c N1 M0) right breast cancer after mastectomy and axillary node dissection in March 2014
- Pathology showed a 1.7 cm invasive ductal cancer, poorly differentiated at grade III (9/9). There was no lymphovascular invasion and margins were negative. ER is 7/8 and PR 6/8 and Her-2 is negative. Three of eight axillary nodes involved (3/8)
- She is referred for discussion of adjuvant systemic therapy……..considered " high risk" and 3rd generation chemotherapy such as FECD x 6 cycles advised

Adjuvant Chemotherapy Summary

- Adjuvant chemotherapy confers significant reduction in recurrences and death from breast cancer
- Decision to recommend adjuvant chemotherapy takes into account the biologic features of the disease as well as stage
- Variety of chemotherapy regimens have confirmed benefit in the adjuvant setting and the use of one particular regimen over another has to be individualized
- Molecular genomic testing may provide more precise prognostic information and tailored predictive information

Adjuvant Endocrine Therapy

Adjuvant Endocrine Therapy

- Endocrine therapy represents the first molecularly targeted therapy for breast cancer
- Targets the ER protein which is present in 70-80% of breast cancers
- Adjuvant endocrine therapy should be considered in all patients with ER-positive breast cancer

EBCTCG Lancet 2005
Effect of 5 years of tamoxifen by age in ER-positive and unknown patients

	Reduction in Annual Odds	
Age (years)	Recurrence	Mortality
<40	44 (+/-10%)	39 (+/-12%)
40-49	29 (+/-7%)	24 (+/-9%)
50-59	34 (+/- 5%)	24 (+/-7%)
60-69	45 (+/- 5%)	35 (+/-6%)
>70	51 (+/-12%)	37 (+/-15%) NB. 20% ER unknown

Adjuvant Endocrine Therapy Options

- SERMs – antagonist to the estrogen receptor in breast cancers eg tamoxifen
- Aromatase Inhibitors (AI) – reduce estrogen levels in postmenopausal women but contraindicated if pre-or perimenopausal

  eg letrozole, anastrozole, exemestane
- Ovarian function suppression (OFS) - using an LHRH agonist eg goserelin or oophorectomies

Adjuvant endocrine therapy - who, what and for how long?

Adjuvant Tamoxifen

- Taking tamoxifen for 5 years prolongs disease-free survival (DFS) and overall survival (OS)
- Tamoxifen for ten years can reduce recurrence and improve survival
- Endocrine therapy of choice for pre- or perimenopausal women

Adjuvant AI: 3 Strategies

- Upfront Adjuvant Therapy
- Sequential following few (2-3) years of tamoxifen
- Extended after 5 years of tamoxifen

Upfront AI

- Beneficial in terms of DFS vs 5 years of tamoxifen but no OS benefit
- The different AIs have similar efficacy and similar toxicities (eg MA. 27 trial)

Sequential Therapy with an AI

- Initial therapy with an AI *or* a few years of tamoxifen followed by an AI are likely equivalent strategies in terms of efficacy

- The BIG 1-98 trial suggested similar outcomes in women taking upfront AI vs tamoxifen followed by AI vs AI followed by tamoxifen
- The TEAM trial showed no differences in outcome if 5 years of exemestane vs 2-3 yrs tamoxifen followed by 2-3 years of exemestane

Trials of Extended AI after 5 years of Tamoxifen

- NCIC MA.17
- NSABP B33
- ABCSG 6a

- Lowers the risk of breast cancer recurrence and contralateral breast cancer and suggestion of an OS benefit in LN positive patients

ASCO Clinical Practice Guideline Update July 2014: Postmenopausal Women

- Aromatase inhibitors offer a modest but significant benefit over tamoxifen in the adjuvant setting
- In this setting, it remains unclear whether upfront aromatase inhibitor therapy is superior to sequencing approach
- High-risk postmenopausal patients should receive an aromatase inhibitor as part of their adjuvant therapy (after 2 years, 5 years, or when off tamoxifen)
- If received 5 years of tamoxifen initially, should be offered continuing tamoxifen or switched to an AI for ten years total adjuvant endocrine therapy.

JCO 28 (23): 3784-3796, 2010
JCO 32:2255-2269, 2014

Summary-Adjuvant Endocrine Therapy

Premenopausal women

-5 years of tamoxifen (Tam)

-Consider 10 years in high risk pts

-Tam or exemestane + OFS x 5 years: to be considered in high risk premenopausal women with premenopausal estradiol levels within 8 months after adjuvant chemotherapy completion especially if age <35

Postmenopausal women

-5 years of an aromatase inhibitor (AI) or

-2-3 yrs of Tam followed by 2-3 yrs AI

-5 years of Tam if low risk or AI intolerant

★ No data yet for 5 years of an AI after initial adjuvant AI

-If received 5 years of Tam initially, consider 5 years of an AI

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  ER is 7/8 and PR 6/8 and Her-2 is negative. Three of eight axillary nodes involved (3/8)
- She received adjuvant systemic chemotherapy and remains premenopausal after chemotherapy.....Patient could now consider Tam for 5-10 years or OFS + Tam/AI x 5 years

Her 2 Positive Breast Cancer

HER2 Gene Amplification Results in HER2 Protein Overexpression

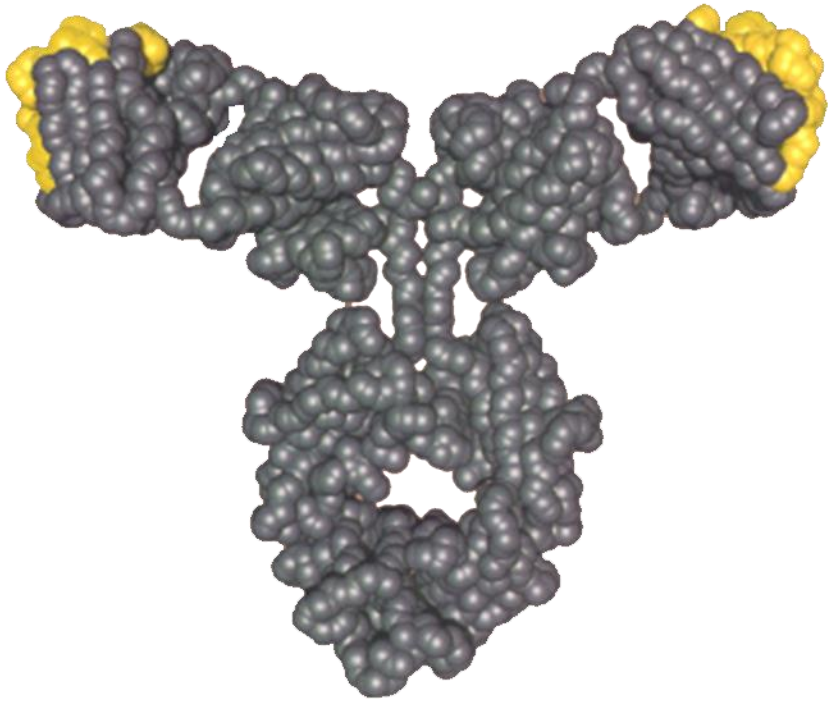
- HER2 overexpression is an independent, negative prognostic factor
- 15% to 20% of breast cancers are HER2 positive
- Two types of tests are most commonly used to determine HER2 status
  - FISH measures the number of copies of the HER2 gene
  - IHC measures the level of expression of the HER2 receptor

HercepTest® package insert, 3rd edition, DAKO; Pauletti et al, *Oncogene* 1996; Pauletti et al, *J Clin Oncol* 2000; Press et al, *J Clin Oncol* 1997; Sjogren et al, *J Clin Oncol* 1998; Sliwkowski et al, *Semin Oncol* 1999

Anti Her-2 Therapy

Trastuzumab

- A recombinant humanized murine antiHer2 monoclonal antibody
- Targets Her2 positive breast cancer cells



Her2 + Adjuvant Trastuzumab Trials

Study	N	Regimen	OS HR p value	DFS HR p value
NCCTG N9831 (LN – incl) and NSABP B31	4045	AC→Taxol +/- H	0.61 <0.001	0.52 <0.001
HERA (LN - incl)	5102	Chemo +/- H (1 vs 2 yrs)	0.75 0.0005	0.76 <0.0001
FinHER	232	D/V→FEC vs D/V+9wksH→ FEC	0.41 0.07	0.42 0.02
PACS 04	528	FEC or ED+/-H	0.86 0.41	1.27 NS
BCIRG 006	3222	AC→D vs AC→DH vs DCH	0.63 <0.001	0.64 <0.001

Her2+ Early Breast Cancer

- "How long"? 1 year of adjuvant trastuzumab reduces breast cancer recurrence by one half and improves survival by one third in combination with chemotherapy
- "Who"? Women with normal cardiac function and with LN+ Her2 positive early breast cancer and for those with LN negative cancers if tumour is greater than 1 cm
- Controversial if T1a or b (1 cm or less) and LN negative but may be considered in T1b N0 setting
- "What"? Several chemotherapy regimens used with trastuzumab including FECD, TC, DCH but because of increased risk of cardiotoxicity of trastuzumab given concurrently with an anthracycline, trastuzumab only given during taxane portion of therapy

Summary

- Adjuvant systemic therapy for early breast cancer can reduce cancer recurrence and improve survival
- Selecting patients for adjuvant chemotherapy is based on risk for cancer recurrence/death and takes into account multiple other factors such as comorbidities, patient preference, etc
- Many adjuvant chemotherapy regimen options but usually use anthracyclines and taxanes and treatments for 4-6 cycles depending on the regimen

Summary cont'd

- All patients with ER + breast cancers should be considered for adjuvant endocrine therapy
- The choice of agent and duration of endocrine therapy depends on menopause status, toxicities/tolerance, risk of cancer recurrence and patient preference
- Adjuvant trastuzumab plus chemotherapy in women with normal cardiac function and tumours > 1cm or LN positive

CancerCare MANITOBA
Action Cancer Manitoba

CCMB Practice Guideline: Disease Management

Provincial Consensus Recommendations for Adjuvant Systemic Therapy for Breast Cancer