A Slow Starvation:
Adjuvant Endocrine Therapy
of Breast Cancer

Dr. Susan Ellard

Surgical Oncology Update
October 24, 2009
Disclosure slide

- Participant in various meetings or advisory boards sponsored by Novartis and Pfizer
- Honoraria deposited to education account for clinical trials staff at BCCA-SI
- CSI has received some funding for breast education initiatives from AstraZeneca
Adjuvant hormone therapy: a long slow siege
Adjuvant chemotherapy: short, nasty and brutal
“siege”

- a military blockade of a city or fortified place to compel it to surrender
- a persistent or serious attack

lay siege to

1: to besiege militarily
2: to pursue diligently or persistently
Targeted biologic therapy?
Outline

- The big picture
- Endocrine therapy then and now…
- Just why are we doing this?
- Something for everyone?
- Who gets what why?
- Surgical precision: nodes, DCIS
- Where are we going from here?

- Summary
Mortality rates by province, per 100,000, women
2009 Canadian Cancer Society estimates

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Figure 4.9
Age-Standardized Mortality Rates (ASMR) for Selected Cancers, Females, Canada, 1980-2009

Note: Rates are age-standardized to the 1991 Canadian population.
Analysis by: Chronic Disease Surveillance Division, CCDPC, Public Health Agency of Canada
Data source: Canadian Vital Statistics Death database at Statistics Canada

Canadian Cancer Statistics 2009
Adjuvant hormones therapy: then and now

Ancient history (when I started on staff in 1997)… to present-day adjuvant practice in BCCA

Then:
- **Adjuvant chemo and hormone therapy**
  - Offered to T2 or greater disease stage if ER/PR+

Now:
- Hormone therapy to any ER+ ca, incl DCIS
- Chemo to any T1c or higher, especially if grade 3
- Trastuzumab, with chemo, to any T1b or higher

Why?
- Because we can….
- …safely!
Flavours of Hormone Therapy

Tamoxifen
- Competes for estrogen receptor
- A weak estrogen in some tissues (bone, uterus, blood vessel)
- EBCCTG: 40% decrease in relapse, 33% decrease in mortality

Ovarian ablation (surgical or chemical):
- for pre-menopausal patients, if problems with Tam, or occasionally in addition to Tam

Aromatase Inhibitors (Anastrozole, Letrozole, Exemestane)
- Block the enzyme which makes estrogen outside of ovary
- Only effective in postmenopausal women
Trials of adjuvant aromatase inhibitors (AIs)

- Conducted because of:
  - Late relapses continuously arising after 5 years of tamoxifen
  - Lack of benefit to > 5 years tamoxifen
  - Slight superiority of AI’s in metastatic setting, compared to tamoxifen
Fig. 1: The double-blind nature of the study was maintained throughout the trial. Dr. Innes is shown sitting.
AI Adjuvant Trial Strategies

- ATAC
- TEAM EXE
- BIG 1-98
- IES
- ITA
- ABCSG/ARNO
- MA-17

End of primary treatment, 2 years, 5 years, 10 years
Upfront AI: 8+ year results of ATAC:

Disease-free survival
HR+ patients

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<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
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<td>HR+</td>
<td>0.85 (0.76, 0.94)</td>
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HR, hazard ratio; CI, confidence interval
NCIC MA17
Disease Free Survival – All Patients

\[ p = 0.00004 \]
IES Trial: Disease-Free Survival

*Absolute difference at 36 months = 4.77. Hazard ratio = 0.68 (95% CI: 0.56–0.82) Log-rank test: $P = 0.00005$. 
Overall Survival

Node Positive

p = 0.04

Node Negative

p = 0.24
Overall survival – ER+ / unknown

End of treatment

Absolute difference at 5 years = 1.4%
(95% CI: 0.1 – 2.5)

Absolute difference at 8 years = 2.4%
(95% CI: 0.1 – 4.8)

HR = 0.86 (95% CI: 0.75 – 0.99); p = 0.04
Caution: Incomparable trials!

- Different patient populations exist at 0, 2.5 and 5 yr entry timepoints

- Exception: BIG 1-98 trial
BIG 1-98 Trial: Recurrence after Upfront AI vs Sequence

Overall

By Nodal Status*

42% Node positives
Side effect and risk differences: Tam vs AI

- **How it feels**: hot flashes, vaginal dryness, sleep change, weight change, transient nausea, achiness

- **How they compare**:
  - Tamoxifen: ? more hot flashes
  - AI: ? more achiness

- **What patients risk**:
  - Tam: slight increase in risk of blood clot, endometrial bleeding, thickening, rarely cancer; ?stroke
  - AI: increased risk for bone thinning, bone fracture; mild rises in lipids, ?CV risks
### Bone risks of AI’s in adjuvant trials

Bone density substudy from ATAC, ASCO 2006

<table>
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<th>Bone density at baseline</th>
<th>Incidence of osteoporosis after 5 yrs anastrazole</th>
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<tr>
<td>Normal</td>
<td>0%</td>
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<tr>
<td>Osteopenia</td>
<td>15%</td>
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- **Remember, BMD ≠ fracture**
- **Some reversibility**
Adjuvant hormone therapy trials

Findings across trials:
- AI-containing regimen reduced relapse risk compared to tamoxifen alone

Remaining questions:
- Does everyone need an AI?
- Which strategy is best?
- Which drug is best?

Answers unknown, but a policy necessary...
Low risk breast cancer: **between year 6 and 10 after diagnosis if free of cancer after 5 yrs of tamoxifen.**  
(BCCA data)

<table>
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<th>Pathologic TMN stage</th>
<th>N</th>
<th>Risk Of Breast Cancer Death</th>
<th>Risk Of Breast Cancer Occurrence (same or new)</th>
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<tr>
<td>Node negative</td>
<td>418</td>
<td>4%</td>
<td>10%</td>
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<td>1-3 nodes positive</td>
<td>380</td>
<td>9</td>
<td>15</td>
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<td>4-9 nodes positive</td>
<td>109</td>
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<tr>
<td>≤ 2cm Tumor</td>
<td>561</td>
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<td>12</td>
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<tr>
<td>2-5 cm Tumor</td>
<td>392</td>
<td>12</td>
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<tr>
<td>T1 N0 Grade 1</td>
<td>42</td>
<td>0</td>
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High risk for relapse within 2.5 years on tamoxifen: BCCA data

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<th></th>
<th>N</th>
<th>2.5 yr relapse rate(%) (95% CI)</th>
<th>P value</th>
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<td><strong>Grade</strong></td>
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<td>I</td>
<td>544</td>
<td>1.1 (0.5-2.5)</td>
<td>&lt; 0.001</td>
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<td>II</td>
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<td>III</td>
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<td>Mod/Hi &gt;50fmol/mg</td>
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<td>6.5 (5.6-7.4)</td>
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<td>Low 10-50 fmol/mg</td>
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<td>14.5 (11.4-18.4)</td>
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<td><strong>Node status</strong></td>
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<td>3.7 (2.9-4.6)</td>
<td>&lt; 0.001</td>
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<td>8.5 (7.3-10)</td>
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<td>18.2 (14.3-20.7)</td>
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BCCA policy for postmenopausal women

- **Tamoxifen x 5 yrs for low risk disease**
  - T1, N0, low grade, no LVI

- **Upfront AI x 5 yrs for high risk disease**
  - Stage 3 &/or grade 3 &/or weak ER+

- Tam for 2.5 yrs then AI for 2.5 years for all the rest

- If premenopausal for >3yrs tam, late switch

- Any AI

- Consider: BMD at baseline and then q2yrs if osteopenic, esp if on > 2-3 yrs therapy
  - Ca 1500 mg, Vit D 1000 IU daily
Cost considerations

- Tamoxifen $180 per 5 years
- AI $150 per month = $1800 per 1 year

↑ cost 50 x for upfront AI x 5 years
Surgical precision

Impact of nodal staging:
- Probably very little impact on adjuvant hormone use
- More impact on use of chemo or not, type of chemo, amount of chemo, radiation or not (to nodes)

Clinical trials
- Currently treat N0 (i+) as N0, not requiring further node dissection
- N1mic as N1, requiring nodal dissection
Al vs tam therapy & risk of 2nd primary Br Ca

- P1 Prevention trial in high risk women (tam v placebo):
  - Tam reduces BrCa risk by ~50%

- ATAC: 20 v 35 pts
- BIG: 0.4% v 0.7% of patients
- MA17: 14 v 26 pts
- IES: 20 v 35 pts

- MA.P3 trial: Exemestane v placebo:
  - underway at CSI and VC—hurry, it’s not too late to refer!!!
MA.P3 prevention trial for postmenopausal high risk women

Eligible:
- Healthy postmenopausal woman > 60
- Or <60 plus Gail score > 1.66
- Or DCIS treated with mastectomy only
- Or LCIS or atypical hyperplasia on any prior biopsy

Gail Score:
- Gail score > 1.66 in almost any postmenopausal woman with a 1st degree relative with Br Ca
Is there anyone who doesn’t receive adjuvant therapy?

- If ER+: if fit, all **offered** hormone adj tx
  - Exception: mastectomy for DCIS
    - eligible for MA.P3 study
  - Partial mastectomy for DCIS
    - many will decline tamoxifen; AI not funded
  - T1N0 and higher
    - Depends on patient preference and estimated risk v benefit

- Triple negative, T1a or b, or chemo-unfit may not have chemotherapy

- HER2+: T1b and higher: low threshold
The things we know we don’t know:

- **Is there a superior AI?**
  - Answer pending, MA27 study

- **Is more or longer therapy better?**
  - SOFT trial in premenopausal women
    - Combination better than tam?
  - NSABP B.42 and MA.17R
    - 8-10 yrs AI vs 5

- **Are other pathways important?**
  - MA33: Metformin v placebo
  - LISA: Impact of lifestyle changes in postmenopause
  - NSABP B43: Brief trastuzumab in HER2+ DCIS, B44?: sunitinib vs placebo in locally advanced, after non pCR
  - MAC.9: iv vs oral bisphosphonates
Summary

- Adjuvant hormone therapy: siege the day
- Spare no one! (almost)
- Tam alone vs AI regimens:
  - A small gain for a big number
- DCIS and primary prevention: AI’s ahead?
- The road ahead: more siege engines?
- Less Mel?
It’s better in BC!!....especially in the Okanagan
Thank you for the invite