Extended Hormonal Therapy

Dr. Caroline Lohrisch,
Medical Oncologist, BC Cancer Agency Vancouver Centre

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Optimal Endocrine Therapy for Women with Hormone Receptor Positive Early Breast Cancer

Dr Caroline Lohrisch
Clinical Associate Professor of Medicine
University of British Columbia
Medical Oncologist, BC Cancer Agency
Vancouver Cancer Centre, BC, Canada

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Disclosures

- Advisory board: Genomic Health; Roche
- Travel grant for CME: Roche
Outline

- Definition of hormone receptor positive breast cancer
- Choices for 5 years of adjuvant hormone therapy
- Extended adjuvant therapy
  - Data for more than 5 years
  - Generalizability to premenopausal women
- Who is at risk after 5 years?
  - Natural history of HR+ breast cancer
  - British Columbia data
- Adjuvant therapy changes since ATLAS, aTTom, Ma17
  - Improvements in chemo, HER2 management, RT
  - Role of ovarian suppression/AI
  - Future therapy possibilities
- Proposed algorithm for duration of hormone therapy
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What is hormone receptor + BC?

**ALLRED SCORING**

- Combined score of % cells staining and strength of staining
- Allred 5/8: 30% cells staining intermediately; OR 10% cells staining strongly
- Clinically, score of 3/8 and 2/8 are considered ER negative
- ER and PR are scored using same system
  - IHC 3+ = Allred 7 or 8
  - IHC 2+ = Allred 5 or 6
  - IHC 1+ = Allred 4 (or 3)
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Adjuvant hormone therapy

Premenopausal
- Tamoxifen
- Tamoxifen (AI) and ovarian ablation
- Ovarian ablation alone

Menopausal
- Tamoxifen
- Aromatase Inhibitor
- Tamoxifen then AI
- AI then tamoxifen

Duration of therapy?
- 5 years
- 10 years
Tamoxifen (T): mechanism of action

Effective in premenopausal and postmenopausal women with ER+ BC

Role in primary prevention; adjuvant therapy; metastatic disease

Partial agonist effects: bone; endometrium; CVS

Estrogen can’t bind

Blockage of signal prevents cell growth; tumor shrinks, cells die

Located in cell nucleus
Benefit of 5 years Tamoxifen

- Magnitude similar in all age groups (<50, 50-69, 70+)
- Effect persists up to 15 years
- Relapses beyond year 5:
  - 16.4% at year 5
  - 25.9% at year 10
5 years of tamoxifen

- 30% relative risk reduction for recurrence
  - Absolute risk reduction 13% NNT 8
- 30% relative risk reduction for death
  - Absolute risk 9% reduction NNT 11
- 50% relative risk reduction for CLBC
- Side effects
  - 1-2% DVT
  - 0.1% endometrial CA (postmenopausal)
  - 40% hot flashes
  - Depression exacerbation in those prone
Aromatase Inhibitors

- Androstenedione
- Testosterone
- Estrone
- Estradiol
- Estrone sulphate

- Postmenopausal women: Major source of total body estrogen
- Premenopausal women: Minor source of total body estrogen

ANASTROZOLE (ARIMIDEX)
LETRIPOZOLE (FEMARA)
EXEMESTANE (AROMASIN)

Reversible inhibitors
Irreversible inhibitor
Adjuvant AI meta-analysis

- Compared with 5 years of tamoxifen:
  - 5 years AI:
    - 3% improvement in DFS
    - 1.1% NON-significant difference in BC-mortality
  - Switch to AI after 2-3 years Tamoxifen:
    - 3% improvement in DFS
    - 0.7% improvement in BC-mortality

  NNT = 33 (instead of 5y TAM)
  NNT =  6 (instead of no hormone therapy)

- DFS = relapse, new CLBC, death from any cause

Dowsett, JCO 2010
ASCO: Postmenopausal women

- ASCO 2004 and 2010 consensus:
  - AI at some point in adjuvant therapy of (all) postmenopausal ER+ BC
  - No recommended “optimal” use of AI (monotherapy vs sequential, or duration)
  - No position on optimal duration of HT
- Who needs (benefits from) the AI?
- Which is the best order to give TAM, AI?
Outline

- Definition of hormone receptor positive breast cancer
- Benefit of 5 years of adjuvant hormone therapy
- **Extended adjuvant therapy**
  - Data for more than 5 years
  - Generalizability to premenopausal women
  - What we don’t know yet
- Who is at risk after 5 years?
  - Natural history of HR+ breast cancer
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Early trials of 5 y vs continuous TAM

Early trials of longer tamoxifen showed no benefit, increased harm

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>EFS</th>
<th>Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stewart</td>
<td>342</td>
<td>Hz 0.73 NS favouring stop</td>
<td>1.7% excess endometrial CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.8% excess CVS deaths</td>
</tr>
<tr>
<td>Fisher</td>
<td>1153</td>
<td>Hz 0.66 (0.58-0.74) favouring stop</td>
<td>1.6% excess endometrial CA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.3% excess VTE</td>
</tr>
<tr>
<td>Tormey</td>
<td>194</td>
<td>85% (tam) v 73% (stop) p0.10</td>
<td>No differences in toxicity</td>
</tr>
</tbody>
</table>

Stewart Br J Cancer 1996; Fisher JNCI 1996; Tormey, JNCI 1996
Modern extended therapy trials

- Tamoxifen for 10 years
  - ATLAS $n=6386$
  - Attom $n=6953$

- AI after 5y tamoxifen
  - MA.17 (letrozole) $n=5187$
  - ABCSG (anastrozole)* $n=862$
  - NSABP B33 ( exemestane)* $n=850$

*underpowered
Modern Extended hormone trials

Absolute reduction in recurrence: 1.5-4.7%

<table>
<thead>
<tr>
<th></th>
<th>MA.17</th>
<th>ABCSG6</th>
<th>ATLAS</th>
<th>ATTOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5187</td>
<td>862</td>
<td>6380</td>
<td>6953</td>
</tr>
<tr>
<td>Drug</td>
<td>L</td>
<td>A</td>
<td>T</td>
<td>T</td>
</tr>
<tr>
<td>Follow up</td>
<td>30</td>
<td>62</td>
<td>120</td>
<td>120 months</td>
</tr>
</tbody>
</table>

MA17: DFS=CLBC, relapse  ABCSG: RFS= relapse or death any  ATLAS, ATTOP: RFS= relapse

Modern extended therapy trials

- Tamoxifen
  - ATLAS 3% OS benefit
  - Attom 3% OS benefit

- AI after 5y tamoxifen
  - Ma.17 (letrozole) 2-4% OS benefit
  - ABCSG (anastrozole)* 4% DFS benefit
  - NSABP B33 (exemestane)* 2% RFS benefit

- NOTE: OS benefit appears earlier for AI than TAM trials

*underpowered
Note the magnitude of benefit is much smaller than for first five years of therapy...making assessment of who is at risk more important to balance QOL and side effects issues.
What about premenopausal women?

- We know:
  - Tamoxifen benefit in first 5y is independent of age
  - Relapse rates over time are independent of age
- aTTom trial: unknown % were premenopausal
- ATLAS: 9% were premenopausal

<table>
<thead>
<tr>
<th>Events/women</th>
<th>10 years events</th>
<th>Ratio of annual event rates (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continue tamoxifen to 10 years</td>
<td>Stop tamoxifen at 5 years</td>
</tr>
<tr>
<td>Age at diagnosis (p=0.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55 years</td>
<td>303/1730 (18%)</td>
<td>354/1729 (20%)</td>
</tr>
<tr>
<td>≥55 years</td>
<td>314/1698 (18%)</td>
<td>357/1689 (21%)</td>
</tr>
<tr>
<td>Menopausal status at ATLAS entry (p=0.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>64/326 (20%)</td>
<td>73/304 (24%)</td>
</tr>
<tr>
<td>Postmenopausal or unknown</td>
<td>553/3102 (18%)</td>
<td>638/3114 (20%)</td>
</tr>
</tbody>
</table>
## What are the harms?

<table>
<thead>
<tr>
<th></th>
<th>Endometrial cancer (postmenopausal)</th>
<th>Pulmonary embolus</th>
<th>Non breast cancer deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATLAS</strong></td>
<td>+ 1.6% (+ 0.2% deaths)</td>
<td>1.3x risk</td>
<td>9% vs 9.5%</td>
</tr>
<tr>
<td><strong>aTTOM</strong></td>
<td>+ 1.6% (+ 0.5% deaths)</td>
<td>NR</td>
<td>13.2% vs 13.4%</td>
</tr>
<tr>
<td><strong>MA.17</strong></td>
<td>1.5% excess risk osteoporosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fracture rates not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No safety data reported beyond 30 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5% excess arthralgias</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Younger women may be at lower risk of ischemic heart disease
- Tamoxifen causes bone loss in premenopausal but is bone protective in menopausal women
- AIs promote bone loss (1% risk of osteoporosis after 5y AI if start with normal BMD); 2% excess fracture risk in adjuvant trials

...SERIOUS RISKS OF LONGER THERAPY APPEAR TO BE LOW AND FEW
What we don’t know yet

- For menopausal women with an AI within the first five years...
  - No published data on benefit of >5 years of therapy
  - Trials of 5y AI after 2-5 years initial AI are fully accrued and in follow up
  - Survival may be more difficult to demonstrate/achieve due to competing mortality in older women
  - Magnitude of DFS benefit with 10y vs 5y is 2-5%
  - Magnitude of DFS benefit with AI vs not in first 5y is 3%....
  - So a DFS or OS benefit is not guaranteed
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Recurrence patterns for ductal and lobular cancers (IBCSG studies)

Majority of recurrences occur in first 5 years, but recurrence curves do not plateau

About 1/3 of recurrences occur >5 years from diagnosis

Event rate in a population will depend on their initial risk:

ATLAS control arm had 25% event rate years 5-10
Recurrence patterns for early breast cancer

Hormone receptor positive
**HER2+ER+ cancers have similar recurrence pattern as ER+ cancers**

BC data, n=3589

known HER2 status

Trastuzumab in 72% of HER2+
Who is still at risk after 5 years?

- Since 70-75% of breast cancers are HR+ and
- Since 75-80% of HR+ breast cancers (in BC) are stage I and II and
- Since recurrence rates for stage I, II breast cancer in first 5 years are between 5-15%:
  - Majority of women will be ‘eligible’ for extended hormone therapy at 5 years
- But who is at risk???
• Grade 3 cancers relapse earlier, grade 1, 2 have steady lower recurrence rate
• ER weakly positive cancers relapse earlier, ER moderate and strong have lower but steady rate
• Nodal burden increases risk: NN 2%/year rate out to 10 years; NP 4-6%/year out to 10 years

Kennecke, Cancer 2008
What are recurrence rates for women after 5 years? (BC data)

- Diagnosis between 1989 and 2004
- Age <50 or 50+ at diagnosis of ER positive, Stage I – III (clinical and/or pathological)
- Referred to BCCA with newly diagnosed disease
- <50: Initial Tamoxifen (without ovarian ablation)
- 50+: initial hormone therapy (any)
- No relapse, subsequent CLBC, or death (any cause) within first 5 years of diagnosis

Lohrisch, SABCS 2013, abs 1538
Examined EFS between years 5-10

- **EFS**
  - Recurrence: local, regional, or distant recurrence
  - Contralateral breast cancer
  - Death without recurrence

- Median follow up: 11 years

**10414 cases**

- **8526 (82%) event free at 5 years**

**N= 1886 <50 years old**
- 1692 premenopausal (90%)
- 147 menopause
- 47 unknown (2%)

**N= 6615 50+ years old**

Event rate in years 5-10: 12.8%

**Note:**
BCSS = OS in premenopausal women
BCSS 10% higher than OS in menopausal women
# Event Free Survival years 5-10

<table>
<thead>
<tr>
<th>Initial stage</th>
<th>N</th>
<th># events</th>
<th>10 year event-free survival estimate &amp; 95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>679</td>
<td>47</td>
<td>94.8 (92.8, 96.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>50+ years</td>
<td>2789</td>
<td>204</td>
<td>94.8 (93.8, 95.6)</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>1007</td>
<td>156</td>
<td>88.3 (86.0, 90.2)</td>
<td></td>
</tr>
<tr>
<td>50+ years</td>
<td>3330</td>
<td>589</td>
<td>86.3 (85.0, 87.5)</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>200</td>
<td>38</td>
<td>80.4 (73.6, 85.6)</td>
<td></td>
</tr>
<tr>
<td>50+ years</td>
<td>487</td>
<td>130</td>
<td>73.8 (69.1, 77.8)</td>
<td></td>
</tr>
</tbody>
</table>

- **Premenopausal**
  - STAGE I: 5% at risk
  - STAGE II: 12% at risk
  - STAGE III: 20% at risk

- **Postmenopausal**
  - STAGE I: 5% at risk
  - STAGE II: 14% at risk
  - STAGE III: 26% at risk

EFS= freedom from recurrence, CLBC, death without recurrence
## 5-10 year risk by stage and grade

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th># events</th>
<th>10 year event-free survival</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 1</td>
<td>225</td>
<td>11</td>
<td>97.3</td>
<td>94.0, 98.8</td>
</tr>
<tr>
<td>grade 2</td>
<td>334</td>
<td>28</td>
<td>93.4</td>
<td>90.0, 95.6</td>
</tr>
<tr>
<td>grade 3</td>
<td>118</td>
<td>8</td>
<td>94.4</td>
<td>88.0, 97.5</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 1</td>
<td>151</td>
<td>15</td>
<td>93.8</td>
<td>87.7, 96.9</td>
</tr>
<tr>
<td>grade 2</td>
<td>496</td>
<td>85</td>
<td>87.7</td>
<td>84.4, 90.4</td>
</tr>
<tr>
<td>grade 3</td>
<td>344</td>
<td>56</td>
<td>87.9</td>
<td>83.8, 91.1</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 1</td>
<td>16</td>
<td>1</td>
<td>90.9</td>
<td>50.8, 98.7</td>
</tr>
<tr>
<td>grade 2</td>
<td>96</td>
<td>24</td>
<td>77.3</td>
<td>66.7, 84.8</td>
</tr>
<tr>
<td>grade 3</td>
<td>75</td>
<td>13</td>
<td>82.6</td>
<td>70.0, 90.3</td>
</tr>
</tbody>
</table>

Risk in year 5-10 for Stage I grade 1, 2 cancers under 10%

For stage I grade 3 and stage II grade 1 cancers, the same may be true (wide CI)
Stage II cancers

Grade had more prognostic import than nodes

Node negative Stage II (all ages)  
Node positive Stage II (all ages)
Stage II: other tested variables

- Strength of ER  \( p=0.66 \)
- Chemotherapy (73% received)  \( p=0.09 \)
- Lymphatic or vascular invasion  \( p<0.001 \)

<table>
<thead>
<tr>
<th>Lymphatic/vascular invasion</th>
<th>10y EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>89.6 %</td>
</tr>
<tr>
<td>Present</td>
<td>82.6 %</td>
</tr>
</tbody>
</table>
Study not controlled for:
- adherence to hormone therapy
- chemotherapy type and radiotherapy
- HER2 status
- changes in adjuvant therapy over time
  - Taxanes
  - Trastuzumab
  - Regional radiotherapy in 1-2 node positive disease
  - Adjuvant aromatase inhibitors

Caveats
Effect on recurrence rates of advances in adjuvant therapy

Cohort 1

1986-1992 treated patients

Cohort 2

2004-2008 treated patients

Cossetti, J Clin Oncol, in press
Impact on EFS of modern era therapy

- Perfect compliance will improve EFS
- EFS improvements of 2-4% in some cohorts

<table>
<thead>
<tr>
<th>Stage</th>
<th>Our cohort</th>
<th>modern EFS rates (y5-10)</th>
<th>Modern changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I, grade 1, 2</td>
<td>97%, 93%</td>
<td>97%, 93%</td>
<td>AI</td>
</tr>
<tr>
<td>Stage I, grade 3</td>
<td>94%</td>
<td>95-96%</td>
<td>Taxanes; trastuzumab; AIs</td>
</tr>
<tr>
<td>Stage II, grade 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>node negative</td>
<td>95%</td>
<td>95%</td>
<td>None</td>
</tr>
<tr>
<td>node positive</td>
<td>92%</td>
<td>94-95%</td>
<td>RT; AIs</td>
</tr>
<tr>
<td>Stage II, grades 2, 3</td>
<td>88%, 88%</td>
<td>90-91%</td>
<td>Taxanes; RT (NP); trastuzumab; AIs</td>
</tr>
<tr>
<td>Stage III</td>
<td>Risk unlikely to drop below 10% except in HER2 +</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Future landscape changes

- LHRH/AI role
- Adjuvant mTOR / hormone therapy in high risk
- Dual anti-her2 in high risk HER2 +
- Palbociclib and others
Other prognostic ‘tools’

21-gene recurrence Score Assay discriminates risk beyond 5 years (ATAC)

- Menopausal population
- Subset of parent study
- Not available for node positive
- Not available >5 years from dx
- Unclear whether predicts benefit

Dowsett, J Clin Oncol 2010
Who to treat:

We know
- There are benefits to longer hormone therapy
  - Tamoxifen for 10 years
  - AI for 5 years after 5y of tamoxifen
- Who is at risk

We don’t know
- Who will benefit
- What to do for women who have
  - High risk and
  - AI within first 5 years
Proposed Algorithm

No recurrence, death, or CLBC at 5 years

Stage I
All ages

5 years: grade 1, 2
Low risk (RS or Similar assay)

5 or 10 years: grade 3
Or intermediate risk (RS or similar assay)

10 years: high risk (RS or similar assay)

Stage II, NN and NP
All ages

5 or 10 years: grade 1
Low risk (RS Assay)

10 years: all grades

Stage III
All ages

10 years: high/intermed

Consider individual Quality of Life, serious toxicities, co-morbidity, prior RX

Premenopausal at 5 years: tamoxifen
Postmenopausal at 5 years: aromatase inhibitor
Thank you for your attention