Use of Ovarian Suppression and Ablation in Breast Cancer Treatment

Dr Marina Parton
Consultant Medical Oncologist
Royal Marsden and Kingston Hospitals
Overview

• Breast cancer phenotypes
• Use of ovarian manipulation as a treatment

• Methods of ovarian suppression
  GnRH analogues
  surgery
  radiotherapy

• Role in early breast cancer (EBC) management
  SOFT/TEXT study
• Role in advanced breast cancer (ABC) management

• Other uses

• Summary

• Case histories

• Questions
Clinical Breast Cancer Subsets

All Breast Cancer

ER+ 65-75%

HER2+ 15-20%

Triple neg 15%
Estrogen Stimulation of Target Tissues

**PRE-menopausal Women**

- **Ovarlan Steroidogenesis**
  - Granulosa
  - Corpus Luteum

  - **AROMATASE**

  - **ESTRADIOL**
    - Target Tissues eg, Breast Breast Tumor

**POST-menopausal Women**

- **Adrenal Gland**
  - **ANDROSTENEDIONE**
  - **AROMATASE**

  - **Adipose Tissue**
  - Liver
  - Breast
  - Breast Tumor

- **ESTRADIOL** → **ESTRADIOL** ↔ **ESTRONE**
Estrogen Stimulation of Target Tissues

**PRE-menopausal Women**

- **Ovarian sup/ablation**
  - Ovarian Steroidogenesis
    - Granulosa
    - Corpus Luteum
  - AROMATASE
  - Tamoxifen
  - Estradiol
  - Target Tissues (e.g., Breast, Breast Tumor)

**POST-menopausal Women**

- Adrenal Gland
  - Androstenedione
  - Aromatase inhibitors (Tamoxifen)
  - Estrone
  - Breast Tumor

- Adipose Tissue
- Liver
- Breast
- Breast Tumor

**Adrenal Gland**

**Aromatase inhibitors** (Tamoxifen)

**Estradiol**

**Estrone**
Biochemical ovarian suppression

• GnRH analogues
  gonadotropin-releasing hormone analogue luteinizing hormone releasing hormone agonist (LHRH agonist) or LHRH analogue

• Synthetic peptides developed to mimic hypothalamic releasing hormone which stimulates FSH and LH

• Agonists used to down regulate FSH and LH long term (flare in release initially) and cause chronic hypogonadism

• reversible
GnRH

- Goserelin (zoladex) sc monthly preparation
- Triptorelin
- Leuprolelin

i.n., injection or implant

Also used in IVF, prostate cancer, endometriosis, uterine fibroids, pubertal growth problems.
Surgical oophorectomy

Dr George Beaston, 1896, Lancet
the first case of advanced breast cancer in a young lactating women who, after mastectomy, responded to surgical removal of her ovaries
survived 4yrs.

Operative risks
Laparoscopic BSO
Irreversible
BRCA carriers- risk reduction
Ovarian irradiation

- Used less commonly now
- Variable schedules, usually outpatient based
- Amenorrhea and falls in E2 may take a while
- Some (esp younger) may resume menses
- SE from pelvic irradiation
Evidence for Ovarian suppression

- Chemotherapy induced amenorrhoea

- Oxford overview
  - In the absence of tamoxifen and chemotherapy, ovarian ablation/OS is of benefit
  - Little difference seen between OS and ablation

- SOFT
Evidence of chemotherapy induced amenorrhoea and outcomes

- Scottish trial
- ZEBRA (Zoladex early Breast Cancer Research Association)
- CALGB

- Improved outcomes in women with ER positive breast cancers when menses stopped.
- Younger women less likely to benefit due to return of menses
Death from all causes
All women < 55 years

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Women</th>
<th>Ratio</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation (absence)</td>
<td>2177</td>
<td>0.79</td>
<td>0.06</td>
</tr>
<tr>
<td>Suppression (absence)</td>
<td>1523</td>
<td>0.90</td>
<td>0.13</td>
</tr>
<tr>
<td>Ablation (presence)</td>
<td>5569</td>
<td>0.99</td>
<td>0.05</td>
</tr>
<tr>
<td>Suppression (presence)</td>
<td>4510</td>
<td>0.92</td>
<td>0.06</td>
</tr>
<tr>
<td>Total</td>
<td>14,122</td>
<td>0.92</td>
<td>0.03</td>
</tr>
</tbody>
</table>

- **(a) Ovarian ablation in the absence of chemotherapy**
  - Ablation (absence): 2177, Ratio: 0.79, SE: 0.06
  - Suppression (absence): 1523, Ratio: 0.90, SE: 0.13
  - Ablation (presence): 5569, Ratio: 0.99, SE: 0.05
  - Suppression (presence): 4510, Ratio: 0.92, SE: 0.06
  - Total: 14,122, Ratio: 0.92, SE: 0.03

- **(b) LHRH inhibitor in the absence of chemotherapy**
  - 0.79 (SE 0.06) reduction, 2p = 0.0002

- **(c) LHRH inhibitor in the presence of chemotherapy**
  - 0.92 (SE 0.06) reduction, 2p < 0.01; NS
  - 0.915 (SE 0.030) reduction, 2p = 0.005

- **95% confidence intervals:**
  - Heterogeneity between 5 subtotals: $\chi^2 = 8.4; p = 0.08$
  - Heterogeneity within subtotals: $\chi^2 = 16.1; p = 0.01; NS$
  - Heterogeneity between 28 trials: $\chi^2 = 24.5; p = 0.01; NS$

§: 5 trials with no data do not contribute to subtotals or to the overall total.
* For balance, control patients in 3-way trials or trial strata count half or twice in subtotal(s) and in final total of deaths/patients.
Question

• ER positive BC
  – Chemotherapy
  – Tamoxifen
  – Is OS also needed??
  – If OS is given- is an AI better then Tamoxifen for pre men women??
The SOFT trial is a randomized, phase III study to evaluate endocrine treatment strategies in pts who remain pre-menopausal after completion of neo-/adjuvant chemotherapy (CTx) or for whom TAM alone is considered the standard of care.

Main inclusion criteria:

- HR+ early breast cancer
- Documented pre-menopausal (pre-menopausal oestradiol level within 8 months after completion of neo-/adjuvant CTx)
- Had completed loco-regional treatment

SOFT trial

Median follow-up 67 months
3066 pts randomized
3047 pts included in ITT analysis
2033 pts included in the ITT primary analysis

No Chemotherapy (47%)
Premenopausal, within 12 weeks of surgery

Prior Chemotherapy (53%)
Premenopausal after completing chemotherapy; Randomization within 8 months of completion

• Primary End Point: DFS (null hypothesis: TAM + OFS would reduce the risk of BC recurrence, second invasive cancer or death by 25%, further 25% risk reduction with E + OFS as compared to TAM + OFS)
• Amended Primary Analysis: TAM vs TAM + OFS (pts enrolled older then expected and lower risk)
• Secondary End Points:
  – Breast cancer disease free interval
  – Distant disease free interval
  – Overall survival

Courtesy of Dr S Redana
## SOFT trial

### End Point Summary

<table>
<thead>
<tr>
<th>End Point</th>
<th>No. of Patients</th>
<th>No. of Patients with Event</th>
<th>5-Yr Rate (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tamoxifen–OS</td>
<td>Tamoxifen</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Disease-free survival</td>
<td>All patients</td>
<td>1015</td>
<td>1018</td>
<td>139</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>Prior chemotherapy</td>
<td>No</td>
<td>473</td>
<td>476</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>542</td>
<td>542</td>
<td>107</td>
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<tr>
<td>Freedom from breast cancer</td>
<td>All patients</td>
<td>1015</td>
<td>1018</td>
<td>120</td>
<td>140</td>
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<tr>
<td></td>
<td>Prior chemotherapy</td>
<td>No</td>
<td>473</td>
<td>476</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>542</td>
<td>542</td>
<td>97</td>
</tr>
<tr>
<td>Freedom from distant recurrence</td>
<td>All patients</td>
<td>1015</td>
<td>1018</td>
<td>89</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Prior chemotherapy</td>
<td>No</td>
<td>473</td>
<td>476</td>
<td>7</td>
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<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>542</td>
<td>542</td>
<td>82</td>
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<tr>
<td>Overall survival</td>
<td>All patients</td>
<td>1015</td>
<td>1018</td>
<td>47</td>
<td>59</td>
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<tr>
<td></td>
<td>Prior chemotherapy</td>
<td>No</td>
<td>473</td>
<td>476</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>542</td>
<td>542</td>
<td>39</td>
</tr>
</tbody>
</table>

Courtesy of Dr S Redana
SOFT trial

350 patients (11.5%) under age 35
94% received chemotherapy in this age group

![Graph showing survival rates and event counts for different treatment groups.](image)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts</th>
<th>Events</th>
<th>5-yr %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>112</td>
<td>34</td>
<td>67.7</td>
<td>57.3 - 76.0</td>
</tr>
<tr>
<td>T+OFS</td>
<td>121</td>
<td>27</td>
<td>78.9</td>
<td>69.8 - 85.5</td>
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<tr>
<td>E+OFS</td>
<td>117</td>
<td>19</td>
<td>83.4</td>
<td>74.9 - 89.3</td>
</tr>
</tbody>
</table>

Courtesy of Dr S Redana
## SOFT trial
### SE of therapy

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Tamoxifen (N = 1006)</th>
<th></th>
<th>Tamoxifen plus Ovarian Suppression (N = 1005)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Event</td>
<td>Grade 3 or 4 Event</td>
<td>Any Event</td>
<td>Grade 3 or 4 Event</td>
</tr>
<tr>
<td></td>
<td>no. of patients with event</td>
<td>% (95% CI)</td>
<td>no. of patients with event</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>803</td>
<td>79.8 (77.2–82.3)</td>
<td>76</td>
<td>7.6 (6.0–9.4)</td>
</tr>
<tr>
<td>Depression</td>
<td>469</td>
<td>46.6 (43.5–49.8)</td>
<td>38</td>
<td>3.8 (2.7–5.1)</td>
</tr>
<tr>
<td>Sweating</td>
<td>486</td>
<td>48.3 (45.2–51.4)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Insomnia</td>
<td>466</td>
<td>46.3 (43.2–49.5)</td>
<td>29</td>
<td>2.9 (1.9–4.1)</td>
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<tr>
<td>Hypertension</td>
<td>173</td>
<td>17.2 (14.9–19.7)</td>
<td>54</td>
<td>5.4 (4.1–6.9)</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>694</td>
<td>69.0 (66.0–71.8)</td>
<td>63</td>
<td>6.3 (4.8–7.9)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>124</td>
<td>12.3 (10.4–14.5)</td>
<td>1</td>
<td>0.1 (0.0–0.6)</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>421</td>
<td>41.8 (38.8–45.0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>427</td>
<td>42.4 (39.4–45.6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Glucose intolerance†</td>
<td>18</td>
<td>1.8 (1.1–2.8)</td>
<td>3</td>
<td>0.3 (0.1–0.9)</td>
</tr>
<tr>
<td>Any targeted adverse event‡</td>
<td>959</td>
<td>95.3 (93.8–96.5)</td>
<td>238</td>
<td>23.7 (21.1–26.4)</td>
</tr>
</tbody>
</table>

 Courtesy of Dr S Redana
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Exemestane plus Ovarian Suppression (N = 2318)</th>
<th>Tamoxifen plus Ovarian Suppression (N = 2325)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Event</td>
<td>Grade 3 or 4 Event</td>
</tr>
<tr>
<td></td>
<td>no. of patients with event % (95% CI)</td>
<td>no. of patients with event % (95% CI)</td>
</tr>
<tr>
<td>Allergic reaction or hypersensitivity</td>
<td>115 5.0 (4.1–5.9)</td>
<td>11 0.5 (0.2–0.8)</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>168 7.2 (6.2–8.4)</td>
<td>1 &lt;0.1 (0.0–0.2)</td>
</tr>
<tr>
<td><strong>Hot flushes</strong></td>
<td><strong>2125 91.7 (90.5–92.8)</strong></td>
<td><strong>232 10.0 (8.8–11.3)</strong></td>
</tr>
<tr>
<td>Depression</td>
<td>1165 50.3 (48.2–52.3)</td>
<td>87 3.8 (3.0–4.6)</td>
</tr>
<tr>
<td>Sweating</td>
<td>1264 54.5 (52.5–56.6)</td>
<td>— —</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1348 58.2 (56.1–60.2)</td>
<td>89 3.8 (3.1–4.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1420 61.3 (59.2–63.2)</td>
<td>73 3.1 (2.5–3.9)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td><strong>527 22.7 (21.0–24.5)</strong></td>
<td><strong>151 6.5 (5.5–7.6)</strong></td>
</tr>
<tr>
<td>Cardiac ischemia or infarction</td>
<td>16 0.7 (0.4–1.1)</td>
<td>7 0.3 (0.1–0.6)</td>
</tr>
<tr>
<td>Thrombosis or embolism</td>
<td>24 1.0 (0.7–1.5)</td>
<td>19 0.8 (0.5–1.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>721 31.1 (29.2–33.0)</td>
<td>17 0.7 (0.4–1.2)</td>
</tr>
<tr>
<td><strong>Musculoskeletal symptoms</strong></td>
<td><strong>2057 88.7 (87.4–90.0)</strong></td>
<td><strong>254 11.0 (9.7–12.3)</strong></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>894 38.6 (36.6–40.6)</td>
<td>10 0.4 (0.2–0.8)</td>
</tr>
<tr>
<td>Fractures</td>
<td>158 6.8 (5.8–7.9)</td>
<td>29 1.3 (0.8–1.8)</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>1214 52.4 (50.3–54.4)</td>
<td>— —</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>1042 45.0 (42.9–47.0)</td>
<td>— —</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>707 30.5 (28.6–32.4)</td>
<td>53 2.3 (1.7–3.0)</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>304 13.1 (11.8–14.6)</td>
<td>6 0.3 (0.1–0.6)</td>
</tr>
<tr>
<td>CNS cerebrovascular ischemia</td>
<td>5 0.2 (0.1–0.5)</td>
<td>4 0.2 (0.0–0.4)</td>
</tr>
<tr>
<td>CNS hemorrhage</td>
<td>15 0.6 (0.4–1.1)</td>
<td>1 &lt;0.1 (0.0–0.2)</td>
</tr>
<tr>
<td>Glucose intolerance†</td>
<td>54 2.3 (1.8–3.0)</td>
<td>11 0.5 (0.2–0.8)</td>
</tr>
<tr>
<td>Hyperglycemia†</td>
<td>61 2.6 (2.0–3.4)</td>
<td>13 0.6 (0.3–1.0)</td>
</tr>
<tr>
<td>Any targeted adverse event</td>
<td>2279 98.3 (97.7–98.8)</td>
<td>710 30.6 (28.8–32.6)</td>
</tr>
</tbody>
</table>
SOFT trial – Proposed action

• Standard of care for most pre-menopausal women is unchanged with chemotherapy, and 5-10yrs of tamoxifen

• Young pts (≤35 years old) receiving neo/adjuvant chemotherapy discussion on OFS + E or TAM is warranted but caution
  – Long term SE likely to be greater
  – Small subgroup analysis

• High risk pts warranting neo/adjuvant CTx (T≥2, node positive, high grade, HER2 positive) should receive adjuvant OFS + E if tolerated or TAM
  – Monitor for bone health and SE management

• For pts experiencing chemotherapy induced amenorrhea
  – Commence TAM
  – oestradiol level monitored at the end of CTx, after 4 months and after 8 months
  – If continue menstruating during CTx, should receive OFS

Courtesy of Dr S Redana
OS/OA and Advanced Breast Cancer (ABC)

• OS and tamoxifen standard of care in ER positive premenopausal ABC

• OS allows premenopausal women to have access to the more recent advances in endocrine therapy eg aromatase inhibitors, targeted agents such as fulvestrnat and palbociclib (in clinical trials now)

• Long term menopausal effects as often patients choose permanent OA
GnRH analogues to preserve fertility during chemotherapy

- Incidence of POF depends on type of chemotherapy and age (10% at <35yrs, up to 85% at >45 years), use of agents such as cyclophosphamide

- Can cause
  - Infertility
  - Osteoporosis
  - Hot flushes
  - Sleep disturbance
  - Sexual dysfunction

- Has a bearing in influencing treatment decisions in 1/3 of cases
- No therapeutic advantage in triple negative breast cancer
Current evidence

- Efficacy of GnRH analogues in preserving ovarian function reported in 12 studies
  - Single arm studies encouraging (including 2 large prospective studies in last 2 years)
  - RCTs data conflicting
  - Heterogeneous populations and procedures
  - Most recent studies supportive of treatment and show no additional risk
- Lack of proven mechanism of action make interpretation difficult
- Appears to be safe in TNBC and ER +ve cancer (smaller studies)
- Sufficient data to use in women routinely if other options limited
Summary

• OS increasingly used in the adjuvant setting to preserve ovarian function during chemotherapy (all types of breast cancer)

• OS/OA plays an increasing role in adjuvant therapy for ER positive disease
  – Long term health (bone, CVS) and SE

• Ongoing expansion of OS/OA in ER positive breast cancer in ABC setting- many women may choose to have OA to enable better access to new targeted agents
  – Long term health (bone, CVS) and SE
• Thank you
Case Hx 1

- 42 yrs old
- 15mm G3 IDC 21/22 I nodes
- ER 8/8 PgR 8/8 HER2neg
- 3rd gen chemo
- RT
- Tamoxifen
- Zoladex+ AI now discussed
Case Hx 2

- 42yrs old
- 15mm G3 IDC 1/22 I nodes
- ER 8/8 PgR 8/8 HER2neg

- 3\textsuperscript{rd} gen chemo
- RT
- Tamoxifen – no change
Case Hx 3

- 35yrs old
- 15mm G3 IDC 1/22 I nodes
- ER 4/8 PgR 6/8 HER2neg

- 3rd gen chemo
- RT
- Tamoxifen- in ER weak tumours gain likely to be very small.