Ovarian Suppression for Premenopausal Women with Breast Cancer

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THE SEVEN DWARVES OF MENOPAUSE

Itchy, Bitchy, Sweaty, Sleepy, Bloated, Forgetful, & Psycho
George Thomas Beatson (1848-1933)

- 1884 - Realizes in rabbits that when ovaries are removed, they stop producing milk
- Also notices that significant changes happen in breast tissue
History

“On the Treatment of Inoperable Cases of Carcinoma of the Mamma. Suggestions for a New Method of Treatment” Beatson, G Lancet, 1896

3 women with breast cancer treated by removing their ovaries

All 3 had a good response, 1 of them, a 33 yo woman, with visual complete resolution of breast tumor
Beatson Institute for Cancer Research
Glasgow University, Scotland
It took 30 years, however, for the discovery of Estrone, the first estrogen, by Edward Doisy in 1929.
INFLUENCE OF SYNTHETIC OESTROGENS UPON ADVANCED MALIGNANT DISEASE

BY

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AND
EDITH PATERSOON, M.B., F.R.C.P.Ed.

WITH AN
ADDENDUM by P. C. KOLLER, D.Sc., Ph.D.

(From the Royal Cancer Hospital (Free), Fulham Road, London, and the Christie Hospital and Holt Radium Institute, Withington, Manchester)
History

In 1946, Charles Huggins demonstrated that in women whose ovaries were removed, estrogen was produced by the adrenal glands and removing them could help treat breast cancer.
3 main types of estrogens:

- **Estradiol (E2)** – most common during reproductive years
- **Estrone (E1)** – most common after menopause
- **Estriol (E3)** – most common during pregnancy
Estrogen

All Estrogens are made from male hormones, androgens

![Chemical structure of testosterone and estradiol](attachment:image.png)

TESTOSTERONE $\xrightarrow{\text{aromatase}}$ ESTRADIOL
Tamoxifen

- First synthesized in 1966, but wasn’t until 1980 that it showed benefit in early stage breast cancer
- Blocks the action of estrogen
Aromatase Inhibitors

- September, 2000 – first AI – Arimidex – FDA approved for breast cancer
- Block production of Estrogen
- 2 types of AI’s
  - Steroidal – exemestane (Aromasin)
  - Non Steroidal – anastrazole (Arimidex) and letrozole (Femara)
Premenopausal women

- Ovaries are working normally and producing estrogen
- Brain can’t tell if the drop in estrogen is because of a block in the action (Tamoxifen) or block in production (AI’s)
- It responds the same way - by increasing FSH
Premenopausal Women

- ↑ FSH = ↑ Estrogen

- If on tamoxifen, then increased estrogen is not an issue as estrogen receptors are blocked

- If on AI, however, then increased estrogen can lead to stimulation of estrogen positive breast cancers
NSABP B30:
- Clinical trial with over 5000 women looking at 3 different chemo regimens
- Found that women who developed amenorrhea had a 50% improvement in survival than those who did not
- This was primarily seen in women with ER+ breast cancer

Should we shut down the ovaries of premenopausal women with breast cancer??
OFS

Methods of Ovarian suppression

Permanent

- Oopherectomy (BSO)
- Pelvic radiation

Temporary

- LHRH agonists
Oophorectomy

- Can be done laparoscopically, open via an abdominal incision, or vaginally (at time of hysterectomy)

- Overall operative risks are low
  - Bleeding or infection
  - Ureteral injury
  - Bowel injury
Ovarian radiation

- Dose is usually 15Gy which is about $\frac{1}{4}$ dose used to treat breast cancer
- 96% - 100% effective
- 4-10 treatments on average
- Can be done during breast radiation
LHRH Agonists

Include leuprolide (*Lupron*), gosarelin (*Zoladex*) and triptorelin (*Trelstar*)

Constant stimulation of LHRH receptors in brain

↓

Less LHRH receptors

↓

Much less FSH and LH secretion

↓

Much less estrogen secretion
OFS and tamoxifen

- EBCTCG meta-analysis from 2007
  - No benefit to adding OFS to tamoxifen except maybe in women under 40 and very high risk patients

- ECOG 3193 (345 women)
  - Tamoxifen vs tamoxifen + OFS
  - No difference in outcomes
Both trials initiated by the IBCSG in collaboration with the BIG/NABCG

TEXT (Tamoxifen and EXemestane Trial)

SOFT (Suppression of Ovarian Function Trial)

Included premenopausal women with ER+ breast cancer with goal of assessing the benefit of OFS when combined with either tamoxifen or exemestane
SOFT Trial

ER+ and/or PgR+.
+ or – Chemo.
Premenopausal
(post chemo if given)

RANDOMIZE

Tam * 5 yrs
OVS + Tam x 5 yrs
OVS + Exe x 5 yrs

OVS = GnRH, oophorectomy, or XRT
(Assumes tamoxifen alone is standard treatment)
Choice of whether to give chemotherapy must be made prior to randomization. Triptorelin to start with chemotherapy. GnRH = Triptorelin, given for at least 6 months, then oophorectomy or XRT allowed.

(Assumes all such patients need ovarian suppression)
# TEXT/SOFT patients

<table>
<thead>
<tr>
<th></th>
<th>TEXT</th>
<th>SOFT</th>
</tr>
</thead>
<tbody>
<tr>
<td># WOMEN</td>
<td>2660</td>
<td>2030</td>
</tr>
<tr>
<td>CHEMO</td>
<td>60%</td>
<td>54%</td>
</tr>
<tr>
<td>NODE +</td>
<td>48%</td>
<td>34%</td>
</tr>
<tr>
<td>HER 2 +</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>AGE &lt; 40</td>
<td>24%</td>
<td>30%</td>
</tr>
</tbody>
</table>
SOFT/TEXT results

Combined analysis of the 2 trials looking at the Tam/OFS vs Exe/OFS groups (NEJM, July 2014)

At 5 years:
- 92.8% of pts in Exe/OFS cancer free
- 88.8% of pts in Tam/OFS cancer free
- Which means a relative improvement in disease free survival of 36% with Exe/OFS vs Tam/OFS
SOFT results

Given current standard of care is tamoxifen alone, the comparison of Tam vs Tam/OFS is important.

What does OFS add to Tam alone in premenopausal women?

<table>
<thead>
<tr>
<th>Population</th>
<th>Tam</th>
<th>Tam/OFS</th>
<th>Exe/OFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer free at 5 yrs</td>
<td>86.4%</td>
<td>88.4%</td>
<td>90.9%</td>
</tr>
<tr>
<td>Did not get chemo</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Got chemo</td>
<td>78%</td>
<td>82.5%</td>
<td>85.7%</td>
</tr>
<tr>
<td>Age &lt;35</td>
<td>67.7%</td>
<td>78.9%</td>
<td>83.4%</td>
</tr>
</tbody>
</table>
## SOFT/TEXT results

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>No. of Patients with Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>5-Yr Disease-free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exemestane–OS</td>
<td>Tamoxifen–OS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All patients</td>
<td></td>
<td>0.72 (0.60–0.85)</td>
<td>91.1</td>
</tr>
<tr>
<td></td>
<td>2346</td>
<td>2344</td>
<td>216</td>
<td>298</td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEXT</td>
<td>526</td>
<td>527</td>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td>SOFT</td>
<td>470</td>
<td>473</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEXT</td>
<td>806</td>
<td>801</td>
<td>93</td>
<td>130</td>
</tr>
<tr>
<td>SOFT</td>
<td>544</td>
<td>543</td>
<td>81</td>
<td>98</td>
</tr>
<tr>
<td>Lymph-node status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1362</td>
<td>1350</td>
<td>70</td>
<td>115</td>
</tr>
<tr>
<td>Positive</td>
<td>984</td>
<td>994</td>
<td>146</td>
<td>183</td>
</tr>
</tbody>
</table>
### Grade ¾ Adverse effects (SOFT/TEXT)

<table>
<thead>
<tr>
<th>ADVERSE EFFECT</th>
<th>EXE/OFS</th>
<th>TAM/OFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot Flushes</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Depression</td>
<td>3.8%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.1%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.5%</td>
<td>7.3%</td>
</tr>
<tr>
<td><strong>Bone/Joint Pains</strong></td>
<td><strong>11%</strong></td>
<td><strong>5.2%</strong></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

- Pts on Exe/OFS reported more vaginal dryness, ↓libido and arousal
- Pts on Tam/OFS reported more hot flushes and sweats
Grade $\frac{3}{4}$ adverse effects (SOFT)

<table>
<thead>
<tr>
<th>ADVERSE EFFECT</th>
<th>TAM</th>
<th>TAM/OFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot Flushes</td>
<td>7.6%</td>
<td>13.2%</td>
</tr>
<tr>
<td>Depression</td>
<td>3.8%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.9%</td>
<td>4.6%</td>
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</table>
Bioidentical hormones

- Loose definitions – molecule identical to that produced by the body
- Claims of “natural” – plant based. In fact all are plant based from soybeans or yams
- Initially developed in the 30’s but rose to fame when Suzanne Somers touted them in 2006
- FDA, American Cancer Society, AMA, Mayo Clinic, etc have said that there is lack of evidence that bioidentical hormones have risks/benefits that are any different than conventional hormones therapy.
So What Should You Do?

Women Age <35
- Chemo or no chemo: OFS+AI

Women Age >35, I start with Tamoxifen
- Got chemo: if after 6 months, no menses, check estradiol/FSH level
  - If postmenopausal: cont Tamoxifen
  - If still premenopausal: OFS + AI or Tam

Did not get chemo (low risk): Tam