

Subcutaneous Testosterone-Anastrozole Therapy in Breast Cancer Survivors

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Abstract 221

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Learning Objectives

After reading and reviewing this material, the participant should be better able to:

- Identify symptoms of androgen deficiency in pre and post menopausal breast cancer survivors
- Recognize the potential role of subcutaneous testosterone-anastrozole implant therapy in safely treating those symptoms

Outline

- Background
- Methods
- Results
- Conclusion
- Future

Background

- Both pre and post menopausal breast cancer survivors commonly experience symptoms of hormone deficiency that can adversely affect their health and quality of life

Efficacy of Testosterone Therapy

- Continuous testosterone therapy, delivered by subcutaneous (SC) implant, effectively treats hormone/androgen deficiency symptoms as measured by the HRQOL, Menopause Rating Scale (MRS) in both pre and post menopausal patients¹

Symptoms improved with SC continuous testosterone therapy

- Hot flashes, sweating
- Heart discomfort
- Insomnia , sleep problems
- Depressive mood, Irritability, Anxiety
- Physical fatigue, Memory loss
- Sexual dysfunction
- Incontinence, bladder problems
- Vaginal dryness
- Joint and muscular pain

Additional potential benefits in breast cancer survivors

- Testosterone protects against bone loss
- Testosterone stimulates bone marrow and enhances immune function

Background

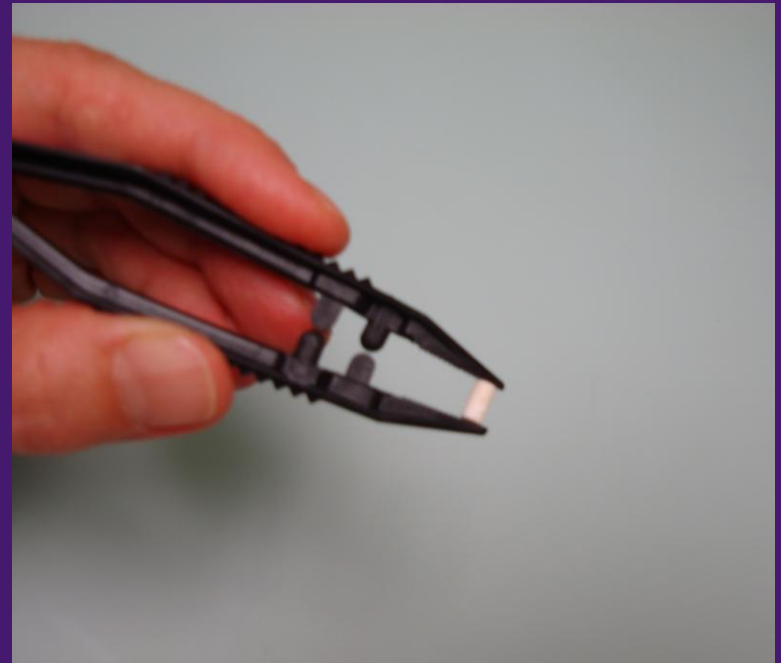
- Evidence supports that testosterone is breast protective^{2,3}
- Testosterone can be aromatized to estradiol which may have adverse effects on breast cancer proliferation
- Third generation aromatase inhibitors effectively inhibit the aromatization of testosterone to estradiol

Preliminary data: 35 male patients

- 12 mg of anastrozole, a third generation aromatase inhibitor (AI), delivered *subcutaneously* by pellet implant, with up to 1200 mg of testosterone, effectively prevented the conversion of testosterone to estradiol in male patients with previously elevated estradiol levels

Subcutaneous delivery (implants)

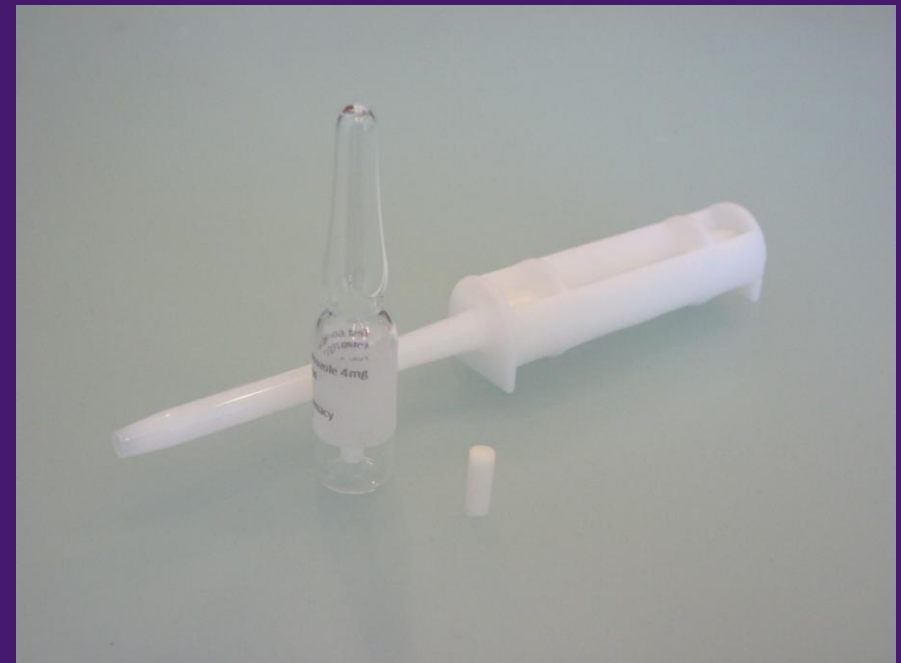
- Consistent delivery and consistent absorption
- Effective therapy
- Avoids entero-hepatic circulation
 - Bypasses liver
 - Does not affect clotting factors
 - Absence of GI side effects
- Circadian release
- No compliance issues
- Well tolerated
- Simple procedure to insert



Testosterone-Anastrozole Implant

- 3.1 x 6.1 mm implant
 - 60 mg testosterone
 - 4 mg anastrozole

Powdered is compressed and sterilized
- Dose females: 2 implants
 - 120 mg testosterone
 - 8 mg of anastrozole



Simple 2 minute Procedure



Methods

- Breast cancer survivors were referred from their oncologists or self-referred (with permission from oncologist) for symptoms of androgen deficiency including bone loss
- Prior to July 2009, oral AI therapy was prescribed in conjunctions with SC testosterone in ER positive patients

Methods

- Data was available on 75 testosterone-anastrozole inserts performed in 43 of 55 breast cancer survivors treated between July 2009 and May 2010

Patient Demographics

- 38/43 patients were > 5 years from diagnosis
- 40/43 tumors were ER pos / non-invasive Ca
- Tumor Stage
 - 8 DCIS, 1 LCIS
 - 19 Stage I
 - 10 Stage II
 - 1 Stage III
 - 4 Stage IV

Methods: procedure, testing

- Two anastrozole-testosterone (A-T) implants (120 mg testosterone, 8 mg anastrozole) were inserted subcutaneously (SC) using local anesthesia in the upper gluteal area
- Serum testosterone and estradiol levels were measured two weeks following implantation

Results (Clinical)

- Subcutaneous testosterone-anastrozole therapy was effective in treating symptoms of hormone/androgen deficiency in breast cancer survivors
- All patients achieved relief of symptoms with therapeutic testosterone levels
 - Mean: 281 ng/dl, range: 120-518 ng/dl

Results

- In 70 of 75 (93.3%) testosterone-anastrozole pellet insertions (43 patients), serum estradiol measured ≤ 30 pg/ml
- A single post-menopausal patient on A-T had an estradiol level >40 pg/ml
 - Subsequent level measured <30 pg/ml

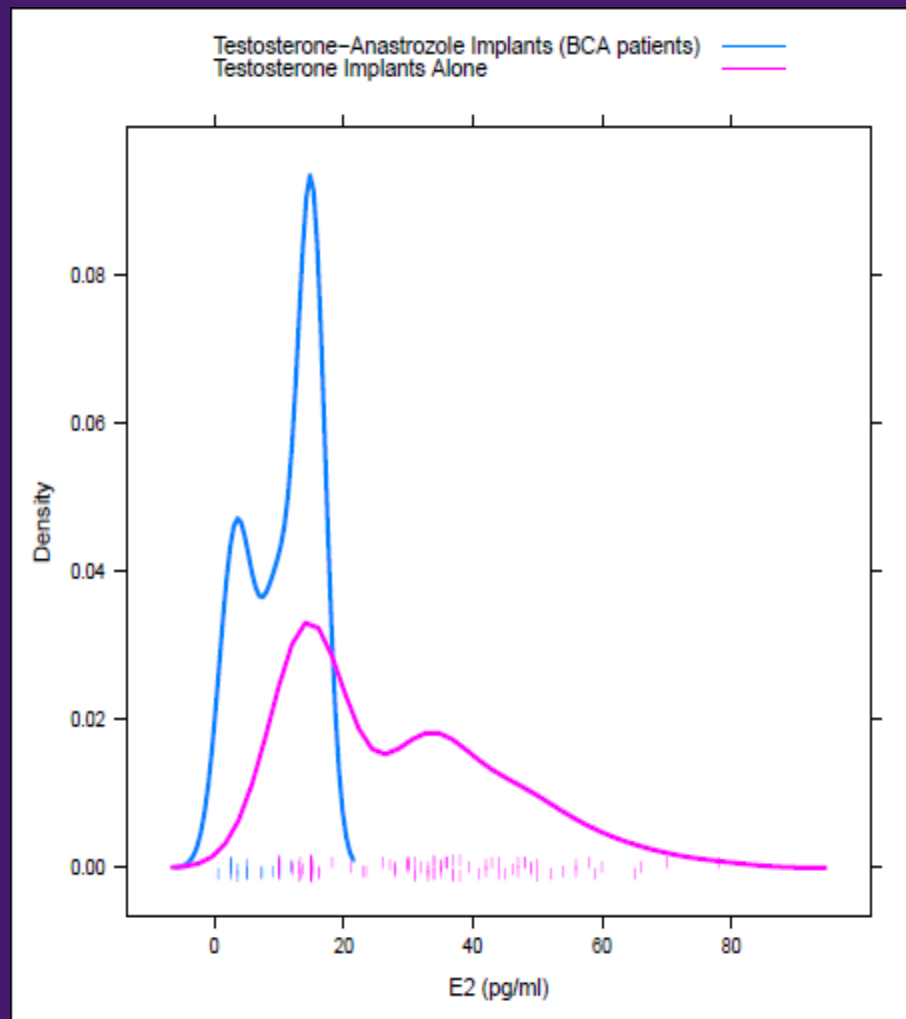
Results: E2 levels T alone vs. A-T

- Control group (n=119)
 - Post menopausal females treated with Testosterone implants alone (T)
- Estradiol levels: T vs. A-T
 - 42% (50/119) of patients treated with Testosterone alone had an E2>30 pg/ml
 - 6.7% (5/75) of patients treated with Anastrozole in combination with Testosterone (A-T) had an E2>30 pg/ml

Estradiol Density Plot

The levels of Estradiol (E2) in the group with the aromatase inhibitor is significantly less than in the group without it (2-sample Wilcoxon rank sum test, $P < 0.0001$).

The separation of E2 in both groups is almost disjoint as illustrated by the kernel density plot.



Clinical follow up

- There have been no adverse drug events in over 170 insertions in 67 breast cancer survivors (Through September 2010)
- No breast cancer survivor treated with subcutaneous testosterone therapy has been diagnosed with recurrent disease in up to 4 years of therapy

Results

- There has been no progression of disease in in 2 ER pos patients and 1 ER neg patient with metastatic disease treated for up to 30 months
 - The 4th patient presented with active disease and has responded to chemotherapy with minimal side effects from the chemotherapy. She continues on therapy and disease is stable.

Conclusion

- The combination of testosterone with anastrozole, delivered subcutaneously as a pellet implant, provides therapeutic levels of testosterone without elevating estradiol levels

Current & Future Studies

- Testosterone Implant-Breast Cancer Incidence Trial (Current) Glaser, Dimitrakakis
 - IRB approved, 10 year prospective study looking at the incidence of breast cancer in pre and post menopausal women treated with subcutaneous testosterone therapy
- ATTICA Breast* Trial (Future) Glaser, Dimitrakakis
 - Randomized, placebo controlled trial treating BrCa survivors on no current therapy, with SC A-T implants

*Anastrozole-Testosterone Therapy in CA Breast
Pending IRB approval and Funding

References

1. Glaser R, Wurtzbacher, D, Dimitrakakis C. Efficacy of Testosterone Therapy Delivered by Pellet Implant. *Maturitas* 2009, 63(Suppl 1);283.
2. Dimitrakakis C, Bondy C. Androgens and the breast. *Breast Cancer Research* 2009;11(5):212.
3. Traish AM, Fettes K, Minor M, Hansen ML, Guay A. Testosterone and risk of breast cancer: appraisal of existing evidence. *Hormone Molecular Biology and Clinical Investigation*. 2010; 2 (1): 177

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