Gynecologic Care for Breast Cancer Survivors

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Case

• 34 yr G2P2 presents with a palpable breast mass – you send her for a FNA which returns positive for carcinoma. She has no other medical history and no family history of breast cancer. She undergoes a lumpectomy for a 1.8 cm infiltrating ductal carcinoma that is ER+/PR+ and Her2Neu negative. She receives adjuvant chemotherapy with AC followed by Taxol, then radiation, and is placed on Tamoxifen. Her menses stop with chemotherapy and return 6 mos later.

Questions

• 1. Is she at risk for endometrial cancer by taking Tamoxifen?
• 2. Will Tamoxifen affect her menses?
• 3. Would you recommend routine ultrasound surveillance?
• 4. Would you send her for genetic counseling to rule out hereditary cause? (BRCA)

Breast Cancer Epidemiology

• Breast Ca most common invasive cancer in US women
• 230,480 new cases invasive Breast ca in US in 2011
• Median age of diagnosis is 61
• 12% diagnosed in reproductive years (ages 20-44)
• More than 25,000 cases per yr in California
• Lifetime risk 1 in 8 at age 85
Breast Cancer Epidemiology

- 2.6 million women living in US with history of Breast Ca

- Breast cancer rates were increasing since 1980 but SEER data showed 2.1% decline in breast cancer incidence per year from 1999 to 2005. Stable from 2005-2008 (.7%)

- Much may be related to drop in HRT use after publication of WHI in 2002, but other factors also likely - frequency of mammography, use of SERM’s (Raloxifene), more aggressive treatment of DCIS, fewer medicare visits

Breast Cancer Epidemiology

- 89% women diagnosed alive at 5 yrs – 98.6% alive for localized breast cancer

- Since 1990, breast cancer mortality has declined, and current declines 2% per year

- Risk of death from Breast Ca 1 in 35

- 40,000 deaths per year


Breast Cancer Treatments

- Breast surgery – either breast conserving lumpectomy or modified mastectomy. May also include immediate or delayed reconstructive procedures

- Radiation

- Chemotherapy

- Hormonal Therapies

These treatments can all have gynecologic effects

Gynecologic Issues Related to Breast Cancer

- Chemotherapy induced menopause

- Gynecologic effects of hormonal therapies

- Treatment of menopausal symptoms
  - Hot flashes
  - Vaginal dryness/discomfort
  - Sexuality issues

- Gynecologic uses of hormonal therapies

- Ovarian suppression
Gynecologic Issues Related to Breast Cancer

- Fertility drugs and breast cancer
- Pregnancy and breastfeeding after breast cancer
- Breast cancer diagnosed during pregnancy
- Hormone replacement therapy after breast cancer
- Ovarian Surveillance: BRCA1/2

Breast Cancer Treatments and Menopause

Menopausal complaints often more severe

- Surgical treatments may include oophorectomy with immediate onset of menopause
- Premenopausal women with normal menstrual functioning get put into immediate menopause with chemotherapy
- Postmenopausal women abruptly stop their hormones when diagnosed with breast cancer
- Side effects of hormonal drugs like Tamoxifen often severe

Chemotherapy Induced Menopause

- Incidence of ovarian failure dependent on chemotherapy regimen, cumulative dose and age of patient
- Most ovarian toxicity due to alkylating agents - cyclophosphamide
  - 33-81% after 6 cycles CMF
- Moderate ovarian toxicity with doxorubicin or cisplatin
- Less ovarian effects with 5-FU, methotrexate, and vincristine
- Less ovarian effects with taxol and taxotere, newer agents and less known regarding longterm effects

Chemotherapy Induced Menopause

- Overall incidence of chemotherapy-induced amenorrhea ranges from 53% to 89%
- 50% women < 35 resume normal menses post chemotherapy
- 70-90% women > 40 have permanent ovarian failure post chemotherapy
- Women who menstruate post chemotherapy still at increased risk for premature menopause
Breast Cancer Tumors

- Breast tumors are all sent for ER/PR status and to see whether over-expression of Her2neu
- Estrogen and Progesterone positivity tells you the tumor will benefit from drugs that manipulate the hormonal environment
- Her2neu- oncogene driven, marker of more aggressive tumor, but does much better since the introduction of anti-angiogenic drug Trastuzumab (Herceptin)

Hormonal Treatments and Breast Cancer

- Used to reduce recurrences and overall breast cancer mortality in women with hormone receptor positive breast cancer
- Biologic goals of hormonal therapy
  - Block production of estrogen
  - Block action of estrogen
  - Down-regulate the estrogen receptor

Hormonal Treatments of Breast Cancer

- SERMS: Tamoxifen, Raloxifene, Toremifene
- Estrogen Receptor Downregulators: Fulvestrant (Faslodex)
- Aromatase Inhibitors: Anastrozole (Arimidex), Letrozole (Pemara), Exemestane (Aromasin)

Hormonal Treatments of Breast Cancer - Tamoxifen

- Complex drug with estrogen and anti-estrogen properties
- Originally made as contraceptive then found to suppress mammary tumors in rats
- By 1992 shown to increase disease free interval and decrease contralateral breast cancer in pre and postmenopausal women
Tamoxifen – What are the Benefits?

- Overview of tamoxifen treatment trials shows that 5 years of treatment decreases the annual risk of recurrence by 41% and annual mortality risk by 34%, independent of age, menopausal status, lymph node status, or chemotherapy use. Similar reductions seen over 15 years of follow up.

- 5 years of adjuvant tamoxifen is standard of care for premenopausal women with hormone receptor positive breast cancer.

Tamoxifen – What about Longer Treatment?

- Many trials have looked at longer treatments – 10 years or more.

- US National Surgery Adjunct Bowel Project and Scottish trials showed lower survival with continued use of tamoxifen beyond 5 years.

- Most of European trials haven showed benefits for extended treatment beyond 5 years.

- Ongoing trials looking at 10 years versus 5: Preliminary results have shown less breast cancer deaths with longer treatment, but more endometrial cancers.

Tamoxifen for Breast Cancer Prevention

- Breast Cancer Prevention Trial showed 5 years of tamoxifen in high risk women reduced risk of hormone receptor positive breast cancer by 45%.

- 7 follow up showed that tamoxifen reduced risk of invasive breast cancer by 57% and noninvasive breast cancer by 63%.

- Approved by FDA in 1998 for breast cancer prevention.

Tamoxifen – Why Don’t More Women Use for Prevention?

- Adverse side effects reported in 60% pts.

- 20-40% discontinue drug because of poor tolerability and effects on QOL.

- Weight gain typically 7-10 lbs.

Common Side Effects:
- Hot Flashes
- Vaginal Discharge
- Vaginal Dryness
- Joint Pain
- Headaches
Tamoxifen – Other Adverse Events

- Increased risks venous thromboembolism, PE and stroke. In NSABP prevention trial:
  - RR 1.6 for DVT
  - RR 3.0 for PE
  - RR 1.59 for stroke
- Updated data show for women who get a stroke, 10% will die and for women with a PE 20% will die

Tamoxifen - Biologic Effects

- Agonist and Antagonist effects
- Effects of Tamoxifen vary depending on hormonal environment

Tamoxifen and Premenopausal Women

- Induces estrogen production and ovulation - has been used for ovulation induction for IVF
- Reports of ovarian cysts in upwards of 30% women
- Case reports of endometriomas - unknown whether induces new endometriosis or exacerbates existing disease
- Growth of endometrial polyps and fibroids
- **NO SIGNIFICANT ESTROGENIC EFFECTS ON ENDOMETRIUM** – only rare reports of endometrial cancers

Tamoxifen and Premenopausal Women - Effects on Menses

- 50% pts have menstrual irregularity - oligo and amenorrhea, but affected by prior chemotherapy
- Pregnancy: Reports of teratogenicity in rodent studies – although series of women who have conceived on Tamoxifen and had normal pregnancy outcomes
- Nonhormonal forms of contraception indicated
Tamoxifen and Postmenopausal Women

- Case reports of growth of fibroids
- Case reports of endometriosis and endometriomas
- Increased endometrial proliferation, cystic changes, polyp formation, adenocarcinoma and uterine sarcoma

Tamoxifen and Endometrial Cancer

- Frequency of cancer dependent on endometrial surveillance: TVS vs. EMB and criteria for surveillance – symptomatic vs. asymptomatic
- The reported risks of endometrial cancer in Tamoxifen users have ranged from 1.3-7.5 in RCT, and increase with longer use
- RR in the US NSAPB trial was 2.53, seen in women > 50

Tamoxifen and Endometrial Cancer

- Absolute risks - about 4 cases of endometrial cancer per 1000 women taking Tamoxifen each year
- 95% of Endometrial Cancers present with Vaginal Bleeding
- Most women get a much greater benefit to their breast than risk to their uterus

Tamoxifen and Uterine Sarcomas

- Sarcomas occur in 2-5% of patients with uterine malignancy
- Sarcomas accounted for 10% of uterine malignancies in NSABP trials
- Overall incidence: 
  - .01 - .02/1000 non Tam users
  - .17/1000 in Tam users (in NSABP)
- Survival from sarcomas not affected by Tamoxifen use
### Tamoxifen and Other Types of Endometrial Cancer

- Recent studies show more aggressive endometrial cancer subtypes including papillary serous, clear cell, and mixed mullerian tumors in Tamoxifen users.
- Review from MD Anderson 2004 showed shorter time to development of endometrial cancer in Tamoxifen users but no difference in outcomes.
- Report in Cancer 2007 from British Columbia Cancer Agency registry showed despite more aggressive subtypes, no difference in endometrial cancer specific survival.
- Overall felt that tamoxifen does not affect endometrial cancer survival.

### Endometrial Surveillance - Ultrasonography

- Increased endometrial thickness, irregular echoes, cystic changes, polyps and hyperplasia in postmenopausal women.
- Findings do not correlate with malignant histology.
- Thickened endometrium can be atrophic. Mechanism may be enlargement of subendometrial glands.
- Ultrasound literature says that endometrial thickness <8mm is normal for women on Tamoxifen, but in general, high false positive rates.
- Should not use endometrial thickness as an indicator for intervention.

### Ultrasound of Patient on Tamoxifen

- Sono-hysterography – useful in distinguishing polyps from cystic endometrium.
- MRI useful for evaluating myometrium but less accurate in looking at intracavitary lesions.
- Limited published data looking specifically at Tamoxifen.
What about Mirena use for women on Tamoxifen?

- Cochrane review to determine effectiveness of Mirena in preventing endometrial hyperplasia, polyps, and adenocarcinoma in pre and postmenopausal breast cancer patients taking tamoxifen
- Looked at only RCT, 2 met search criteria
- Results:
  - Mirena led to significant reduction in the incidence of endometrial polyps OR 0.14
  - Neither trial powered to detect changes in the rate of endometrial hyperplasia or adenocarcinoma or whether Mirena led to any increased risk of breast cancer recurrence.
  - More vaginal bleeding in the Mirena treatment group in the first six months only
- Many oncologists feel uncomfortable based on risks of progestins

Tamoxifen – ACOG Guidelines 2006

- Postmenopausal women should be monitored closely for endometrial hyperplasia or cancer
- Premenopausal women do not have increased risks for uterine cancer and should receive routine gyn care
- Women should be informed about risks of Tamoxifen and abnormal vaginal bleeding, or bloody discharge should be evaluated
- Consider pretherapy screening (get baseline ultrasound)
- Routine surveillance is not recommended
- If atypical endometrial hyperplasia develops, patients should receive appropriate treatment (hysterectomy)

Tamoxifen and CYP Testing

- Tamoxifen is converted into its active metabolites in the liver by the CYP2D6 liver enzyme, part of the P450 detoxification pathway
- CYP2D6-mediated drug metabolism is highly variable. 7-10% of individuals have altered CYP2D6 gene sequences that result in decreased enzyme production
- Polymorphisms associated with CYP2D6 poor metabolizer status are autosomal recessive

Tamoxifen and CYP Testing

- Concern whether poor metabolizers may not benefit from tamoxifen and have increased risk for recurrence
- Testing for CYP is commercially available
- Trials have not yet shown that CYP testing is clinically useful, so unclear whether clinical management should not be based on CYP results
**Tamoxifen vs. Raloxifene for Breast Cancer Prevention – STAR Trial**

- STAR trial: 5 years, one of largest breast cancer prevention studies, took place at more than 500 centers in US, Canada, and Puerto Rico
- Tamoxifen reduces risk of invasive breast cancer and DCIS by about 50%
- Recent data from 81 mos of follow up (Apr 2010): Raloxifene is 75% as effective as Tamoxifen in preventing invasive breast cancer and had significantly fewer endometrial cancers, significantly fewer thromboembolic events and fewer cancers.
- Raloxifene was about 78% as effective as Tamoxifen in preventing noninvasive breast cancers.
- Raloxifene is FDA approved for breast cancer prevention in PMP women

**What do All of these things have in common?**

- The first bowel movement after hemorrhoid surgery
- Reading glasses
- A new bra
- A box that arrives at your work the day after your husband or wife forgets your anniversary
- The 2 for 1 sale that lets you get 60 rolls of toilet paper from Costco
- Sitting through the rest of this lecture when you are waiting for your weekend to have an early start

**Hopefully……**

- They give you more value than you might have expected

**Aromatase Inhibitors**

- Tamoxifen competes with estrogen at receptor binding site in the breast preventing receptor activation
- Aromatase Inhibitors prevent conversion of androstenedione and testosterone into estrogens and decrease peripheral circulating estrogen
- Not useful in premenopausal women because blocking aromatase in the ovaries results in lower estradiol levels which reduce negative feedback and increase pituitary gonadotropin output, increasing ovarian function
Aromatase Inhibitors

- Initially first generation AI's used – Aminoglutethimide
  - Inhibited production of all adrenal steroids so needed to be given with hydrocortisone
  - Significant toxicity limited use
- Third generation AI's first approved for metastatic breast cancer
  - Found superior to Tamoxifen
  - Orally administered
  - Less toxicity

Aromatase Inhibitors

- Third generation AI's used:
  - Anastrozole (Arimidex)
  - Letrozole (Femara)
  - Exemestane (Aromasin)
  \[\text{Nonsteroidal - reversible}\]
  \[\text{Steroidal - irreversible inhibitors}\]

Aromatase Inhibitors in Early Breast Cancer
Anastrazole, Tamoxifen, Alone or in Combination Trial (ATAC)

Anastrazole, Tamoxifen, Alone or in Combination (ATAC) trial

- 9000 PMP women with early stage breast cancer, treated with 5 yrs of Anastrazole vs. Tamoxifen, first interim analysis presented in 2001 with now 10 years of follow up.
  - Anastrazole had improved Disease Free Survival (HR .90 at 100 mos)
  - Anastrazole had improved time to recurrence (HR .81 at 100 mos)
  - Anastrazole had lower incidence of contralateral breast cancer (HR .68 at 100 mos)
- No differences in survival
Anastrozole vs. Tamoxifen - Adverse Effects

- **Worse with AI:**
  - More arthralgia, myalgia, and bone loss with AI
  - Increased cardiovascular risks with AI, but no difference in MI, or MI related death
  - Increase risks of fracture in AI group during treatment but not seen after completion
  - More colorectal and lung cancers with AI, not significant
  - More vaginal dryness, dyspareunia and decreased libido in AI group

- **Better with AI:**
  - Fewer CVA in AI group but did not persist after treatment
  - Lower thromboembolic events with AI
  - Fewer endometrial, ovarian cancer and melanoma in AI - only significant for endometrial cancer

- Aromatase Inhibitors may PREVENT endometrial cancer

Aromatase Inhibitors - 2011

- Many international trials have now shown efficacy of Aromatase Inhibitors in adjuvant treatment for postmenopausal women
- FDA approved Anastrozole (Arimidex) as first-line adjuvant therapy in PMP women with hormone positive breast cancer
- FDA approved Letrozole (Femara) for extended adjuvant use in women with early-stage, hormone-receptor-positive breast cancer after five years of tamoxifen
- Gyneologic side effects generally less with AI treatment – fewer hot flashes, but much more vaginal dryness

Aromatase Inhibitors – Gynecologic Uses

- Ovulation Induction – studies have shown pregnancy rates similar to gonadotropins
- Ovulatory Dysfunction – PCOS. Meta-analysis of 4 published trials showed pregnancy rates similar to Clomiphene
- Treatment of Pelvic Pain and Endometriosis – aromatase is expressed at higher levels in endometriosis implants than in normal endometrium. Letrozole and Norethindrone reported to improve symptoms and histologic diagnosed endometriosis – No RCT compared to standard medical therapies
- Treatment for Fibroids – documented aromatase in myoma cells

Common Questions – Who Should get MRI Screening for Breast Cancer?

- New MRI Recommendations: American Cancer Society has recommended annual breast MRI for the following high-risk groups:
  - Women with a BRCA1 or BRCA2 mutation
  - Women who have a first-degree relative with a BRCA mutation (even if they have not yet been tested themselves)
  - Women who have a 20-25% or greater risk of breast cancer based on risk assessment tools (which utilize family history)
Common Questions – Who Should get MRI Screening for Breast Cancer?

- Mammography reports now often state whether MRI recommended
- What about dense breasts? - Newer risk assessment tools likely use breast density as risk factor

Breast Cancer – What’s New in 2011?

- **Individualized Treatment** - Advances in gene expression technologies improves predictions of prognosis and treatment benefit. Oncotype DX and mammoprint are genomic tests that predict risk of cancer recurrence and likely benefit from adjuvant chemotherapy. Future breast cancer treatment will likely become more individualized.

Ovarian Suppression and Ablation

- Ovarian ablation oldest form of systemic treatment for breast ca, first described 1896
- Methods – Surgical, Radiation-Induced, Medical with GNRH analogs (Zoladex)
- Many studies looking at ablation as adjuvant therapy

Overview of trials:

- Ovarian suppression (OS) and ovarian ablation (OA, via surgical oophorectomy) thought to decrease risk of recurrence and improve survival in women < 50 with hormone positive tumors
- Ovarian suppression is thought to be comparable to benefit from adjuvant chemotherapy or tamoxifen alone
Ovarian Ablation with Chemotherapy and Endocrine Therapy

- Unclear if ovarian suppression needed for entire 5 year course of Tamoxifen
- Current trials (TEXT, SOFT) looking at ovarian suppression ongoing to determine optimal hormonal therapy for premenopausal women with early breast cancer

Should the Ovaries Come Out?

- Although data showing ovarian suppression is beneficial, not clear that oophorectomy should be done in all premenopausal women with hormone positive breast cancer
- Counterbalancing risks of subsequent heart disease with oophorectomy in early stage breast cancer

Ovarian Suppression and Fertility

- Preliminary studies looking at ovarian suppression prior to chemotherapy in hopes of preserving ovarian function, mixed results
- Most fertility programs focusing on assisted reproductive techniques to preserve fertility – ovarian stimulation with Tamoxifen or Letrozole and embryo cryopreservation, ovarian tissue or oocyte cryopreservation

Treatment of Vaginal Dryness in Breast Cancer Patients

- Water based lubricants for sexual activity
- Vaginal Preparations of Estrogens or Testosterones thought to increase vaginal blood flow, improve tone and maintain vaginal moisture: creams, ointments, gels
- Vaginal Estring - a slightly opaque ring placed into the vagina for 3 mos - contains a reservoir of 2 mg estradiol which releases approx. 7.5 µg estradiol/24 hours, in a consistent stable manner over 90 days – felt minimal systemic absorption
- Vagifem - vaginal tablet containing 25 µg estradiol inserted 2x per week with minimal systemic absorption – comparable benefit to conjugated equine cream (premarin)
Replens and Vaginal Dryness

- Vaginal Moisturizer Replens - Several studies showing improvement in vaginal itching, irritation and dyspareunia - equivalent to vaginal estrogen creams.
  - Bygum A & Svahn, Maturitas (1996)

- Replens in breast cancer populations - found improvement in vaginal dryness and pain during intercourse, with most of the beneficial effects within the first 2 weeks of treatment and sustained benefit.
  - Pinkerton & Santen, Endoc Rev (1999)
  - Loprinzi et al., J Clin Oncol (1997)

Final Thoughts......

- Common questions about breast cancer -

Do Fertility Drugs increase the risk of Breast Cancer? - NO

- Case-control study in US - no increased risk except for human menopausal gonadotropin (hMG) for > 6 months or 6 cycles
  - Fertil Steril, 2003

- Israeli cohort showed no increased risk except for women treated with clomiphene citrate
  - Breast Cancer Res Treat, 2006

- Large Danish cohort showed no association
  - Cancer Epidemiol Biomarkers Prev, 2007

- Israeli cohort of IVF found women over age 40 and those who underwent > 4 cycles had a higher risk of breast cancer

- Large British cohort with ovulatory disorders showed higher risk of primary breast cancer but no increased risks with fertility drugs
  - Br J Cancer, 2009

Is it safe to get pregnant after having Breast Cancer? - YES

- Large population registry studies have shown no increased risks of recurrences for women who get pregnant after prior treatment for breast cancer

- Typically recommended to wait at least 2 years from diagnosis

- Pregnancies more often in women with early stage breast cancer so possible selection bias “healthy mother effect”
Can I breastfeed if I’ve had Breast Cancer? - MAYBE
• Most patients report inadequate lactation in affected breast
• May have asymmetric breasts due to inadequate hypertrophy
• Breast conserving surgeries may allow for lactation
• Less likely with:
  – Centrally located tumors
  – If prior radiation - induces fibrosis of lobules with decreased milk production

Can I use HRT if I’ve had Breast Cancer? – NOT RECOMMENDED
• Review from Germany showed four prospective randomized studies and 15 observational studies looking at HRT after breast cancer available. Only the Hormonal replacement therapy After Breast cancer Is IT Safe (HABITS) study showed an increased risk of recurrence. Pt samples in studies are small so alternatives recommended
• HRT and ERT and breast cancer complicated: new studies using estrogen therapy to reverse acquired antihormonal resistance in the treatment of metastatic hormone positive breast cancer

Case
• 34 yr G2P2 presents with a palpable breast mass – you send her for a FNA which returns positive for carcinoma. She has no other medical history and no family history of breast cancer. She undergoes a lumpectomy for a 1.8 cm infiltrating ductal carcinoma that is ER+/PR+ and Her2Neu negative. She receives adjuvant chemotherapy with AC followed by Taxol, then radiation, and is placed on Tamoxifen. Her menses stop with chemotherapy and return 6 mos later.

Questions
• 1. Is she at risk for endometrial cancer by taking Tamoxifen? NO
• 2. Will Tamoxifen affect her menses? MAYBE
• 3. Would you recommend routine ultrasound surveillance? NO
• 4. Would you send her for genetic counseling to rule out hereditary risks (BRCA) YES
Hopefully now, you will….

- Know more facts about breast cancer
- Understand the gyn issues related to the treatment of breast cancer
- Understand when Tamoxifen and Aromatase Inhibitors are used in breast cancer treatment
- Understand the gyn implications of Tamoxifen and the Aromatase Inhibitors
- Know about the role of ovarian suppression in breast cancer
- Know about fertility drugs and breast cancer
- Know about safety of pregnancy and hormone use after breast cancer
- Know something new about breast cancer that you didn’t know before this talk….