Quality of Life for Breast Cancer Survivors

Vasomotor Symptoms and Vulvovaginal Atrophy

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Breast cancer survivors constitute the largest group of female cancer survivors. The diagnosis of this cancer greatly impacts menopausal and sexual issues for these women. Although gynecologists are not the primary treaters of this disease, we must provide the expertise to manage the hormonal sequelae of therapy, such as vasomotor and atrophic symptoms, in breast cancer survivors.

Survivorship is fast becoming an important concept in caring for cancer patients. With the great strides made in curing or significantly controlling many cancers, oncologists are now dealing with quality of life issues for survivors. The most common female cancer with long-term survival is breast cancer. Since medical oncologists are not typically trained in menopause and sexual issues, it falls to the gynecologist to care for these women.

We as gynecologists see several categories of breast cancer survivors. We see young premenopausal women rendered menopausal by chemotherapy. There are post- and perimenopausal women on hormone therapy who stop after their diagnosis. We all see relatively minimally symptomatic women whose

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therapy (such as estrogen blockers or aromatase inhibitors) induces vasomotor symptoms. Menopausal symptoms can begin quite abruptly in women in the first two categories above, and the symptoms usually occur on top of multiple other stressors.[1,2]

Conflicts can arise among caregivers. Breast surgeons and oncologists tend to view all estrogen therapies with suspicion, but they are often unfamiliar with alternative medications and their side effects. Even some gynecologists are unfamiliar with alternative menopausal therapies. Further, patients are often reluctant to complain about treatment or its bothersome side effects. The typical comment voiced is, "I should be happy to be a survivor." So they often do not complain of treatment-related side effects. The ancient aphorism *Primum non nocere; secundum bene facere* (first, "do no harm"; second, "do good") should satisfy all caregivers.

FOCUSPOINT➤

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Vasomotor Symptoms

Lifestyle Alterations

Most simple lifestyle alterations are admirable; they should help reduce the risks of recurrence and may help menopausal symptoms. Smokers and obese women tend to have relatively more hot flashes; smoking cessation and weight reduction may help.[3] Ethanol is a known trigger for hot flashes; however, many women actually try to alleviate hot flashes with alcohol. Also, moderate alcohol intake (eg, 2 glasses of wine a day) is known to be a risk factor for breast cancer. Therefore, encouraging patients to limit their alcohol intake should help to decrease their vasomotor symptoms and minimize the risk of disease recurrence.

Complementary and Alternative Choices

As nonpharmacologic treatments typically do little harm, such intervention may be worthwhile because little risk is involved.[4] There is limited data showing that paced respiration, acupuncture, and yoga help to treat hot flashes, with some data in cancer survivors as well.[5,6]

Soy therapy poses a special conundrum for breast cancer survivors. In the literature, there are questions on the efficacy of the use of soy and isoflavones for therapy of hot flashes. However, the literature on soy breaks down into two camps. There are some who believe that because isoflavones act at the estrogen receptor, they can trigger growth of breast tumors. On the other hand, there are also papers suggesting that these isoflavones act as selective estrogen receptor modulators, or SERMs, and block the action of more potent estrogens on any breast cancer cell. The prevailing philosophy on the benefits of soy and isoflavones continues to change over time,[7-10] so it is best to discuss this with your patient and then let her discuss use of soy with her oncologist for approval.

Black cohosh is widely used in Europe in breast cancer survivors. One of the problems in the United States is the nonuniformity of products, which engenders questions on efficacy. There have also been safety questions raised, which have prompted debates on whether black cohosh had estrogenic activity. Research has now shown that this activity was related to estrogenic contaminants.[11-13] Pure products have been shown to produce no increase in breast density and no endometrial stimulation.

Some European studies suggest a therapeutic effect of black cohosh, including lengthening the time to recurrence of cancer in black cohosh users. Laborato-

ry studies have shown that black cohosh treatment may decrease local estrogen formation in breast tissue in vitro, with increased apoptotic activity.[14-16] Discussing this data with medical oncologists may make them more receptive to the use of black cohosh as a treatment option for vasomotor symptoms.

Nonestrogenic Medical Options

SSRIs and SNRIs

Originally used in men with prostate cancer who were treated with gonadotropin-releasing hormone agonists, the selective serotonin reuptake inhibitors (SSRIs) have been shown to reliably reduce hot flashes. Many cancer patients may be dealing with depressive issues as well, and although we may be prescribing SSRIs for vasomotor symptoms, we may also be helping with their depression if present. In general, relief from hot flashes occurs much more rapidly than antidepressant activity with SSRIs and at much lower dosages.[17]

Certain SSRIs can pose metabolic issues to breast cancer patients. Tamoxifen is metabolized into its active form, endoxifen, by the cytochrome P450 2D6 (CYP2D6) enzyme. Paroxetine and fluoxetine can inhibit this enzyme. Venlafaxine has less of an inhibitory effect on plasma levels of endoxifen.[18]

Unfortunately, SSRIs and serotonin/norepinephrine reuptake inhibitors (SNRIs) may be accompanied by unwanted side effects, such as decreased libido and weight gain. Many menopausal women in general complain about decreased libido. Body image issues often accompany a breast cancer diagnosis. This constellation of side effects may be problematic with breast cancer survivors, and they need to be addressed when SSRIs are to be initiated for vasomotor therapy.[19]

Gabapentin

Gabapentin was introduced into our armamentarium to treat hot flashes almost a decade ago. It has reasonable efficacy; most consider a dose of 900 mg daily to be of help. Again, one must consider the side effects in this vulnerable group; bloating, weight gain, and sedation are the major side effects one encounters with gabapentin therapy. It is reasonable to start with a low dose and to titrate up.[20,21]

Treatments for Vasomotor Symptoms in Breast Cancer Survivors

Lifestyle Interventions

- Layer clothing
- Keep room cool at night
- Decrease smoking (smokers have more hot flashes)
- Lose weight (heavier women have more hot flashes)
- Avoid known triggers (such as wine)

Complementary/Alternative Medicine

- Soy (check with oncologist; some oncologists might counsel patients to avoid soy)
- Black Cohosh
  Standardized brand: Remifemin one 20-mg tablet twice daily

Vaginal Therapies Over-the-Counter

- Replens: insert one 3 times weekly
- Lubricant
  Astroglide kit: use at time of sex

Medications

- SSRIs/SNRI
  Venlafaxine, 37.5 g/75 g once daily
  If not on tamoxifen:
  Fluoxetine, 20 mg once daily
  Paroxetine, 10-20 mg once daily
- Vaginal Estrogens
  Vagifem tablets: vaginal tablets estradiol hemihydrate
  1 tablet vaginally daily for 2 weeks; then 1 twice weekly 10 µg of estradiol
- Estring: 2 mg release 7.5 micrograms/day of estradiol for 90 days
- Cream
  Estrace (estradiol), 0.1 mg estradiol/gram
  Premarin (conjugated estrogens), 0.625 mg/gram
  Topically, insert 1 g vaginally daily as needed

Hormonal Therapy

Progestational Agents

Progestational agents have been used for many years for vasomotor symptom relief,

as an alternative to estrogens. Megestrol acetate, in a dosage of 20 to 40 mg/day, has been used with good effects. Depo medroxyprogesterone acetate has also been quite effective. Epidemiologically, no increased risk of breast cancer has been demonstrated when progestin-only therapy has been used. However, the role of progestational agents in women with a history of breast cancer is still unclear.[22-25]

Estrogen

Young practitioners probably do not realize that high-dose estrogens were actually used to treat breast cancer many years ago. Several US studies by gynecologic oncologists have shown no increased risk of recurrences of breast cancer in survivors treated with estrogen therapy for vasomotor symptoms.[26] However, several European studies do show increased recurrences in breast cancer survivors treated with hormonal therapy.[27] The difference in findings may be related to the use of estradiol in the European studies as well as the studies not controlling for tamoxifen use in the study populations.

Vulvovaginal Atrophy

Along with vasomotor symptoms, atrophy is the most common menopausal symptom encountered by breast cancer survivors. All practitioners should be attuned to the sexual and body issues previously discussed. All menopausal breast cancer survivors should be asked about dryness problems; simple validation of their concerns can help these women.

Most women need education on the differences between moisturizers and lubricants; many women will require both. Even women who are not sexually active may need extra moisture vaginally for comfort. Nonhormonal polycarbophil products are available over the counter.

Validation of your patient's concerns is very important; just asking her if she is experiencing discomfort is helpful. Many women appreciate a discussion about over-the-counter lubricants. Referring patients to popular "nontraditional" websites can also alleviate women's embarrassment in exploring sexuality enhancement options (eg, vaginismus.com; passionparties.com).

Vaginal Estrogens

Vaginal estrogens are extremely effective in providing atrophic relief. They are available in the forms of vaginal tablets, rings, and creams. Good data is available on systemic absorption. When first treating very atrophic tissue, there will be some minimal absorption of estrogen systemically. However, this absorption decreases after the vaginal tissue is better estrogenized, increasing blood estrogen levels basically by less than 1 pg/mL.[28] Nonetheless, some oncologists do get anxious even with that data, particularly if their patient is being treated with an aromatase inhibitor and not an estrogen blocker, such as tamoxifen. You may need to speak with your patient and her oncologist to reassure them both on the safety of vaginal therapy.[29,30]

Also remember that there is "class labeling" on all estrogen products, whether they are being sold for systemic use or local use. You will need to mention this to your patients as they read the accompanying package inserts on their vaginal estrogen product to reassure them about the minimal absorption of the vaginal product.

The Future: BRCA-Positive Women

With expanding genetic testing, we will all be seeing more women who are being tested and diagnosed as BRCA-positive and having oophorectomies and mastectomies at very young ages. There is good data emerging that it is safe (and healthful) to treat these women with systemic estrogen.[31] This also brings up the question, in counseling these women, as to whether they should consider a hysterectomy as well as an oophorectomy. Although more surgically complex, if they do have a hysterectomy, they will not need progestin therapy. Of course,

individualized management is required in making these decisions with your patient. (For women with Lynch syndrome, a hysterectomy should be performed.)

Prophylactic Therapy

Some of our patients who are at high risk for breast cancer are currently being treated with tamoxifen or raloxifene for risk reduction. Some of these women do get vasomotor symptoms, which can be addressed as we do for breast cancer patients. However, most oncologists do not have a concern in treating these women with vaginal estrogens for atrophic symptoms when they do develop.

Recently, a paper was published on the use of aromatase inhibitors for prophylaxis.[32] These medications have a significantly higher likelihood of inducing menopausal symptoms, including atrophy, and oncologists are more likely to want to avoid vaginal estrogen therapy in these women. These medications also have a side effect profile associated with bone loss and generalized arthritic symptoms. Gynecological input remains a valuable component of comprehensive patient care for our patients at risk for breast cancer who are considering these options for cancer prevention.

Summary

We are always sorry to see a woman who has been diagnosed with breast cancer but take delight in seeing her surviving and doing well. It is incumbent on all gynecologists to address vasomotor symptoms and atrophic issues in breast cancer survivors, which are huge quality-of-life problems for many such patients.

Addressing these complaints legitimizes them and allows the patient to discuss them with you freely. Not addressing these concerns does not make them disappear. Fortunately, we do have options for therapy that are both safe and efficacious.

The author reports having served as a consultant for Bayer, Enzymatic Therapy, Noven, Novo Nordisk, and Pfizer.

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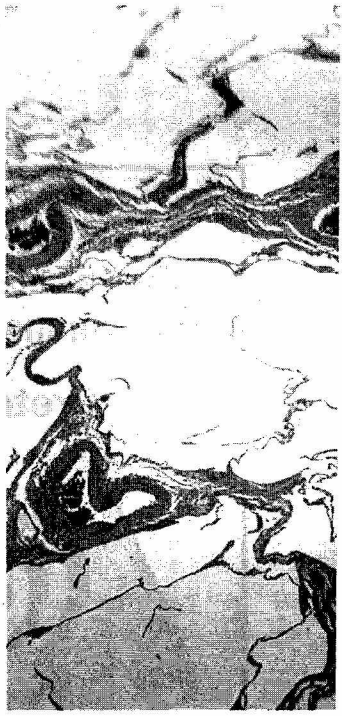

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