

# EPEEC-O

Education in Palliative and End-of-life Care - Oncology

## **Participant's Handbook**

Module 3n:

**Symptoms –**

**Menopausal**

**Symptoms**

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## Case\*

F.A. is 47-year-old married woman who comes to you for an outpatient consultation for advice related to menopausal symptoms that have troubled her since starting tamoxifen adjuvant therapy about one year ago. She was diagnosed with stage II breast cancer (ER/PR positive; 5 nodes positive) about 2 years ago and received a lumpectomy followed by 4 cycles of doxorubicin and cyclophosphamide and 4 cycles of paclitaxel adjuvant therapy. After completing her adjuvant chemotherapy, she received 6 weeks of radiation therapy to the breast and was subsequently started on tamoxifen 20 mg/day.

Prior to starting her chemotherapy, she had been menstruating regularly and had not had any perimenopausal symptoms. She stopped menstruating after 2 cycles of chemotherapy. She had moderately severe hot flashes and night sweats, as well as sleep disturbance, but these got better over the next 6 months. However, once she started the tamoxifen, the severity and frequency of the hot flashes increased and she is now considering discontinuation of tamoxifen. She also reports vaginal dryness and pain with intercourse that began shortly after starting chemotherapy and has gotten worse over the past 2 years. She has tried using a lubricant, but still experiences discomfort. She also reports significant lack of interest in sex and difficulty with arousal. Her husband has been supportive, but she feels saddened by the changes in their intimate relationship.

\* This case is not on an EPEC-O Curriculum trigger tape.

## Introduction

Premature menopause is common in the setting of adjuvant therapy for breast cancer.<sup>1,2,3,4</sup> This situation occurs in female patients with other cancer diagnoses who receive cancer treatment, especially with alkylating agents prior to menopause, although limited data are available for non-breast cancer sites. The primary treatment of breast cancer is already quite complex, and premature menopause imposes an additional burden on younger women.<sup>5</sup> In addition, some women will also note important changes in libido and sexual functioning.<sup>6,7,8</sup> Urinary incontinence can also occur. Women treated for breast cancer today can expect long-term survival, and it is important for clinicians to become familiar with common symptoms that are a result of cancer treatment and premature menopause, and to have strategies to use in their management.

## Prevalence

Menopausal symptoms are less common in women older than 60 years.<sup>9</sup> Menopausal symptoms are not commonly troublesome for women with breast cancer who are already postmenopausal when diagnosed. Rather, they usually occur in the setting of withdrawal of exogenous hormone therapy or in women who receive endocrine therapy, eg, tamoxifen, aromatase inhibitors, who are within a few years of the menopause.

## Prognosis

The outlook for women with cancer treatment-induced menopause is generally good, in that the symptoms associated with menopause—although sometimes abrupt in onset—will eventually resolve in almost all cases with time. Sexual difficulties may get worse, but careful attention to maintaining a good partnered relationship, treatment of anxiety or depression if present, management of sex-related symptoms, eg, dyspareunia, and education about the normal age-related changes and sexual health can help women and their partners through this transition and maintain sexual functioning into the future.

## Pathophysiology

Menopause occurs when a previously menstruating woman with an intact uterus and ovaries has had amenorrhea for at least 12 months. The average age of menopause in North American women is 51 years.<sup>10</sup> Endocrine disorders or conditions can lead to secondary amenorrhea. Cancer treatment-induced secondary amenorrhea is the most relevant consideration in this setting. The menopausal transition is characterized by decreased responsiveness of the ovaries to luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Gradually, over time, the estradiol levels fall as the ovarian follicles are depleted and there is no further response to LH and FSH. Clinical symptoms of estrogen deficiency begin to occur with these changes. Lowered levels of estradiol affect various target tissues, including the vagina, skin, bone, vascular endothelium, and smooth muscle, as well as the hypothalamic temperature-regulating centers.<sup>11</sup> The ovaries are the primary source of androgens in women, persisting into postmenopause, and decreased production of ovarian androgens may account for changes in libido during this time.<sup>12</sup> Symptoms associated with estrogen deficiency include vasomotor symptoms (hot flashes, sweats, palpitations), urinary incontinence, and vaginal dryness. Vasomotor symptoms are most frequent (up to 75% of menopausal women) and are among the earliest symptoms of menopause, with the more gradual onset of urinary incontinence and vaginal dryness in the later postmenopausal years.<sup>11</sup>

The impact of menopause on sexual health is controversial because many women remain sexually active into old age. Several population-based studies of perimenopausal and menopausal women have documented that most women who have partners are sexually active;<sup>13</sup> however, changes can occur in sexual functioning (desire, arousal, orgasm) that are age related and to which menopause may contribute.<sup>11,14,15</sup> Research suggests that in postmenopausal women, a variety of factors are potential moderators of the components of sexual functioning, eg, psychological distress, quality of the partner relationship, physical activity, body mass index.<sup>13</sup> Without sufficient levels of endogenous estrogen, the vaginal epithelium becomes atrophic, leading to clinical symptoms of vaginal dryness and dyspareunia. With chronic or untreated symptoms of vaginal dryness, postmenopausal women often choose to avoid sexual intercourse completely. Hormone replacement therapy is effective in managing menopausal symptoms, such as hot flashes and vaginal dryness, but does not appear to improve sexual functioning.<sup>16,17</sup> Untreated

vaginal dryness can contribute to dyspareunia, thus affecting both desire and arousal in women with cancer. The variety of physical, psychosocial, and treatment-related factors associated with cancer treatment may also cause or exacerbate sexual dysfunction.

Menopause *per se* may not be the culprit.

Tamoxifen and aromatase inhibitors are associated with vasomotor symptoms.

Tamoxifen can also cause vaginal discharge in 10-20% of women due to its estrogenic effects on the vagina, while the aromatase inhibitors are associated with vaginal dryness.

## Assessment

The hot flash or flush is the hallmark menopausal symptom. It is usually described as the sudden sensation of warmth over the face, neck, and upper trunk. It is often associated with sweating and palpitations. Hot flashes may occur infrequently throughout the day or night, or occur nearly continuously in some circumstances. Night sweats, a parallel symptom, are also common in association with the menopause. Sometimes women will also experience nighttime awakening, without a hot flash. These symptoms often appear within a year or two before the last menstrual period and then gradually resolve over several years after the last menstrual period. In women who become acutely menopausal as a result of chemotherapy or the use of ovarian suppression therapy, the intensity and frequency of these vasomotor symptoms can be extreme. In addition, women receiving endocrine therapies at the time of the perimenopause or early menopause will usually have exaggerated vasomotor symptoms.

Most women understand what a hot flash is or feels like. One can ask:

- Are you having hot flashes or sweats? How frequently?
- Do you need to change clothing or change the sheets?
- Do your hot flashes interfere with your activities?
- Do they awaken you at night?

For sexual difficulties, it is important to take a brief history to determine the pattern of sexual difficulties and whether they are related to the breast cancer treatment or menopause. Changes in sexual frequency and patterns are a normal part of aging, although many individuals have an active sex life into old age.

Vaginal examination may show evidence of irritation and friable tissue, and vaginal cytology may show an absence of estrogen effect. While these clinical signs are valuable, their absence does not preclude substantial clinical symptomatology.<sup>18</sup>

The laboratory diagnosis of menopause is usually made with low levels of estradiol in the face of elevated levels of gonadotropins. For women who complain of lack of sexual interest or decreased libido, causes may include: testosterone deficiency, fatigue, anxiety, and depression. Consider ordering a serum free testosterone level as part of the evaluation of sexual dysfunction. Women who have had an oophorectomy, and in some women who

have had chemotherapy, the levels will be exceedingly low and they may warrant testosterone supplementation.

## Management

There are a variety of hormonal and non-hormonal approaches to the management of menopausal symptoms in cancer survivors.<sup>19,20,21,22,23</sup>

### Hormonal therapy

For those women who do not have an estrogen associated cancer, eg, patients with leukemia, lymphoma, etc., systemic hormone therapy can be considered. Give it for as short a period as possible, given the modest level of lack of other benefits and presence of some risks from such therapy.<sup>24</sup> In women with a history of breast cancer, consider a range of hormonal and non-hormonal therapies.

Megestrol acetate is usually quite effective. Its use is limited by theoretical concerns of patients and physicians about the potential risk of a progestational agent in the initiation and promotion of primary breast cancer.

- Megestrol acetate, 20 mg PO bid

### Non-hormonal therapy

Various SSRI antidepressants have also been found to be useful, although recent studies have raised concerns about drug interactions with tamoxifen.<sup>25,26,27</sup>

- Venlafaxine, 37.5mg PO daily for 1 wk then escalate to 75 mg PO daily
- Fluoxetine, 20 mg PO daily

Gabapentin has also recently been found to be effective for hot flash management.

- Gabapentin, 300 mg PO nightly. Titrate to effect, maximum of 900 mg PO q 8 h

### Sleep disturbances

For women with only nocturnal difficulties, either a sleeping medication or a combination with phenobarbital and ergotamine (Bellergal) is occasionally useful.

- Bellergal, 1 tablet PO q 12 h

Most women, however, are reluctant to try medication unless their symptoms are quite severe and for that reason, practical interventions including avoidance of hot liquids or stimulants (coffee, alcohol), layering of clothing to keep cool, and having a fan available are usually helpful.<sup>22,23</sup>

## Vaginal dryness

Vaginal dryness may be a problem with or without adjuvant treatment for breast cancer, as the frequency of this symptom increases with age.<sup>14</sup> The non-hormonal vaginal lubricants, eg, K-Y jelly, Astroglide, Replens, have been found to be helpful in several series. More recently, topical estrogen therapy with a silastic ring implanted with estradiol, has become popular because of the lack of systemic absorption and good relief over a 3 month period of time. Other vaginal estrogen preparations can be considered, however, they may lead to systemic estrogen absorption which may have adverse consequences in terms of breast cancer recurrence.

Vaginal dryness and pain with intercourse may indirectly affect sexual interest, for if coitus is painful, then it may lead to avoidance. If the patient has a good partner relationship, then often some simple suggestions will be helpful in refreshing the relationship and improving the situation. However, it is often useful to refer the couple for sex therapy counseling to address specific issues that may be impairing a satisfying sexual relationship.

### Summary

Menopausal symptoms are often quite troublesome and add to other symptoms that patients experience in relationship to the cancer or its treatment. Their satisfactory control can improve aspects of quality of life and improve sexual functioning, eg, management of vaginal dryness. Often, patients will be reluctant for ask for help with these symptoms, so it is important for the clinician to directly inquire about these symptoms to determine whether or not they are a problem.

### Key take-home points

1. Ask about menopausal symptoms.
2. Treat hot flashes aggressively if the patient finds them disturbing.
3. Ask about vaginal dryness and sexual dysfunction.

### Pearls

1. Sexual function in women with breast cancer is improved when menopausal symptoms are decreased.
2. Therapy for some target menopausal symptoms (hot flashes, vaginal dryness) is effective for the majority of symptomatic women.

### Pitfall

1. Avoiding discussing sexual function out of a sense of modesty.

## References

- <sup>1</sup> Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *J Clin Oncol*. 1996;14(5):1718-1729. [PMID: 8622093](#).

This group attempts to: (1) define menopausal status in the setting of adjuvant chemotherapy; (2) define chemotherapy-related amenorrhea (CRA); (3) document rates of permanent amenorrhea, temporary amenorrhea, and oligomenorrhea among different regimens; and (4) analyze variables that influence ovarian function.
- <sup>2</sup> Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol*. 1999;17(8):2365-2370. [PMID: 10561298](#). [Full Text](#)

Age and systemic chemotherapy are identified as the strongest predictors of menopause in women with locoregional breast cancer. A graphic representation of our multivariate model allows an estimation of risk of menopause according to patient age and planned adjuvant treatment, and it may facilitate clinical decision-making.
- <sup>3</sup> Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast Cancer in Younger Women: Reproductive and Late Health Effects of Treatment. *J Clin Oncol*. 2003;21(22):4184-4193. [PMID: 14615446](#). [Full Text](#)

This is the report of a cohort study to evaluate quality of life (QOL) and reproductive health outcomes in younger female breast cancer survivors.
- <sup>4</sup> Nystedt M, Berglund G, Bolund C, Fornander T, Rutqvist LE. Side Effects of Adjuvant Endocrine Treatment in Premenopausal Breast Cancer Patients: A Prospective Randomized Study. *J Clin Oncol*. 2003;21(9):1836. [PMID: 11387349](#). [Full Text](#)

This study evaluated the sexual effects of the 2-year adjuvant goserelin alone, tamoxifen alone, and Zoladex and tamoxifen in combination (ZT) versus no adjuvant endocrine therapy among premenopausal breast cancer patients with or without chemotherapy in a controlled clinical trial.
- <sup>5</sup> Ganz PA. Menopause and breast cancer: symptoms, late effects, and their management. *Semin Oncol*. 2001;28(3):274-283. [PMID: 11402437](#).

This article will describe what is known about the impact of menopause on breast cancer survivors, focusing on short-term symptoms and other late effects.
- <sup>6</sup> Ganz PA, Rowland JH, Desmond K, Meyerowitz BE, Wyatt GE. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. *J Clin Oncol*. 1998;16(2):501-514. [PMID: 9469334](#).

This cross-sectional study describes the health-related quality of life (HRQL), partner relationships, sexual functioning, and body image concerns of breast cancer survivors (BCS).
- <sup>7</sup> Meyerowitz BE, Desmond KA, Rowland JH, Wyatt GE, Ganz PA. Sexuality following breast cancer. *J Sex Marital Ther*. 1999;25(3):237-250. [PMID: 10407796](#).

This article provides sex and marital therapists with detailed, multifaceted descriptions of sexuality after breast cancer based on survey responses from 863 breast cancer survivors.
- <sup>8</sup> Berglund G, Nystedt M, Bolund C, Sjoden PO, Rutqvist LE. Effect of endocrine treatment on sexuality in premenopausal breast cancer patients: a prospective randomized study. *J Clin Oncol*. 2001;19(11):2788-2796. [PMID: 11387349](#). [Full Text](#)

This study evaluated the sexual effects of the 2-year adjuvant goserelin (Zoladex [Zeneca AB, Sodertalje, Sweden]) alone, tamoxifen alone, and Zoladex and tamoxifen in combination (ZT) versus no adjuvant endocrine therapy among premenopausal breast cancer patients with or without chemotherapy in a controlled clinical trial (a European multicenter trial: Zoladex in Premenopausal Breast Cancer Patients).

- <sup>9</sup> Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Clin Oncol*. 1999;17(9):2659-2669. [PMID: 10561339](#). [Full Text](#)

This report provides an overview of HRQL findings, comparing tamoxifen and placebo groups, and advice to clinicians counseling women about the use of tamoxifen in a prevention setting.

- <sup>10</sup> McKinlay SM. The normal menopause transition: an overview. *Maturitas*. 1996;23(2):137-145. [PMID: 8735352](#).

The review systematically addresses the following aspects of menopause research: definition of menopause and menopause transitions; age at natural menopause and at inception of perimenopause; factors affecting timing and length of menopause transitions; concurrent hormone, menstrual and vascular changes.

- <sup>11</sup> Greendale GA, Lee NP, Arriola ER. The menopause. *Lancet*. 1999;353(9152):571-580. [PMID: 10028999](#). [Full Text](#)

Menopause, its physiology, clinical manifestations and treatment are reviewed.

- <sup>12</sup> Braunstein GD. Androgen insufficiency in women: summary of critical issues. *Fertility and Sterility*. 2002;77(4):94-99. [PMID: 2007911](#). [Full Text](#)

Critical issues concerning the role of androgens in the physical, sexual, and emotional health of women are reviewed.

- <sup>13</sup> Greendale GA, Hogan P, Shumaker S, Postmenopausal Estrogen/Progestins Intervention Trial (PEPI) Investigators. Sexual Functioning in Postmenopausal Women: the Postmenopausal Estrogen/Progestins Intervention (PEPI) Trial. *Journal of Women's Health*. 1996;5:445-458.

- <sup>14</sup> Ganz PA, Day R, Ware JE, Jr., Redmond C, Fisher B. Base-line quality-of-life assessment in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial. *J Natl Cancer Inst*. 1995;87(18):1372-1382. [PMID: 7658498](#).

Base-line quality-of-life of women enrolled in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial is presented.

- <sup>15</sup> Thirlaway K, Fallowfield L, Cuzick J. The Sexual Activity Questionnaire: a measure of women's sexual functioning. *Qual Life Res*. 1996;5(1):81-90. [PMID: 8901370](#).

This study reports psychometric data showing that the SAQ is a valid, reliable and acceptable measure for describing the sexual functioning of women in terms of activity, pleasure and discomfort.

- <sup>16</sup> Myers LS, Dixen J, Morrissette D, Carmichael M, Davidson JM. Effects of estrogen, androgen, and progestin on sexual psychophysiology and behavior in postmenopausal women. *J Clin Endocrinol Metab*. 1990;70(4):1124-1131. [PMID: 1690746](#).

To assess the role of gonadal steroids in sexual behavior in aging women, this group conducted a 10-week, double-blind, hormone replacement study of 40 naturally menopausal women (mean age, 58.3 yr).

- <sup>17</sup> Sherwin BB. The impact of different doses of estrogen and progestin on mood and sexual behavior in postmenopausal women. *J Clin Endocrinol Metab*. 1991;72(2):336-343. [PMID: 1846872](#).

This study investigated the effects of various doses of estrogen and progestin on psychological functioning and sexual behavior of 48 healthy, naturally menopausal women.

- <sup>18</sup> Greendale GA, Zibecchi L, Petersen L, Ouslander JG, Kahn B, Ganz PA. Development and validation of a physical examination scale to assess vaginal atrophy and inflammation. *Climacteric*. 1999;2(3):197-204. [PMID: 11910597](#).

This cross-sectional study evaluated the validity and reproducibility of selected vaginal examination findings proposed to represent vaginal atrophy and inflammation.

- <sup>19</sup> Hoda D, Perez DG, Loprinzi CL. Hot flashes in breast cancer survivors. *Breast J*. 2003;9(5):431-438. [PMID: 12968972](#).

This article reviews the current strategies for the management of hot flashes in breast cancer survivors and the evidence supporting their use.

- <sup>20</sup> Loprinzi CL, Abu-Ghazaleh S, Sloan JA, vanHaelst-Pisani C, Hammer AM, Rowland KM, Jr. et al. Phase III randomized double-blind study to evaluate the efficacy of a polycarbophil-based vaginal moisturizer in women with breast cancer. *J Clin Oncol*. 1997;15(3):969-973. [PMID: 9060535](#).

The present trial was developed to evaluate the nonhormonal vaginal lubricating preparation, Replens, for alleviating these symptoms.

- <sup>21</sup> Loprinzi CL, Barton D. Estrogen deficiency: In search of symptom control and sexuality. *J Natl Cancer Inst*. 2000;92(13):1028-1029. [PMID: 10880537](#). [Full Text](#)

Editorial re Ganz et al. report that the use of a nurse practitioner, in a tailored comprehensive menopausal assessment intervention program, led to a statistically significant decrease in menopausal symptoms and a statistically significant improvement in sexual function in women compared with a group of women without such intervention who served as a control group. The pharmacologic interventions used in this study for hot flashes were Bellergal, clonidine, and megestrol acetate. SSRI antidepressants, not used in this study, has recently demonstrated efficacy for alleviating hot flashes by 50-60%.

- <sup>22</sup> Ganz PA, Greendale GA, Petersen L, Zibecchi L, Kahn B, Belin TR. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *J Natl Cancer Inst*. 2000;92(13):1054-64. [PMID: 10880548](#). [Full Text](#)

The purpose of this study was to test the efficacy of a comprehensive menopausal assessment (CMA) intervention program in achieving relief of symptoms, the improvement in quality of life (QOL), and sexual functioning in breast cancer survivors.

- <sup>23</sup> Zibecchi L, Greendale GA, Ganz PA. Continuing education: Comprehensive menopausal assessment: an approach to managing vasomotor and urogenital symptoms in breast cancer survivors. *Oncol Nurs Forum*. 2003;30(3):393-407. [PMID: 12719740](#).

This article describes the development and implementation of a comprehensive menopausal assessment (CMA) and intervention program for women with a history of breast cancer.

- <sup>24</sup> Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333. [PMID: 12117397](#). [Full Text](#)

This randomized prevention trial evaluated the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

- <sup>25</sup> Loprinzi CL, Kugler JW, Sloan JA, LaVasseur BI, Barton DL, Novotny PJ, Dakhil SR, Rodger K, Rummans TA, Christensen BJ. *Lancet*. 2000;356(9247):2059-2063. [PMID: 11145492](#).
- <sup>26</sup> Loprinzi CL, Sloan JA, Perez EA, Quella SK, Stella PJ, Mailliard JA, Haylard MY, Pruthi S, Novotny PJ, Rummans TA. *J Clin Oncol*. 2002;20(6):1578-1583. [PMID: 11896107](#).
- <sup>27</sup> Stearns V, Johnson MD, Rae JM, Morocho A, Novielli A, Bhargava P, Hayes DF, Desta Z, Flockhart DA. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst*. 2003;95(23):1758-1764.