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Breast Cancer Survivorship Issues

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SURVEILLANCE OF SURVIVORS OF BREAST CANCER

In the 1980s, it was common to follow early stage survivors of breast cancer with multiple blood tests, chest radiographs, and other imaging (eg, bone scans). This practice was not evidence-based, and arose primarily from clinician biases. When patients are followed on clinical protocols with histories, physical examinations, chest radiographs, blood work, and bone scans, approximately 75% of recurrences are first recognized by history or physical examination.¹ In the other 25% of patients, approximately a third of recurrences are each detected by abnormalities in chest radiographs, bone scans, and liver function tests. Virtually no recurrences are identified based on complete blood count abnormalities. Although blood work or imaging may identify the first evidence of distant recurrence in a minority of cases, this is only clinically important if detecting these recurrences while a patient is still asymptomatic improves quantity or quality of life (QOL).

In the 1990s, American Society of Clinical Oncology (ASCO) developed practice guidelines regarding follow-up surveillance in patients with a history of breast cancer that had been treated for cure.² These guidelines were largely influenced by two Italian studies that prospectively evaluated more intensive surveillance strategies, compared with following a patient by history, physical examination, and mammography.^{3,4} These ASCO guidelines were updated, predominantly unchanged, in 2006⁵; they state that the primary surveillance procedures for asymptomatic survivors of breast cancer should include intermittent patient histories and physical examinations every 3 to 6 months during the first 3 years, every 6 to 12 months during years 4 to 5, and annually thereafter; and annual mammography for patients with residual breast tissue, with the first one scheduled at least 6 months after completion of breast radiation therapy. Patients should be educated with regard to symptoms of breast cancer recurrence, and they should be instructed to call a provider if questions or problems arise. Genetic counseling should be offered to those whose personal or family

history is suggestive of a genetic cancer syndrome. Regular gynecologic follow-up is recommended for most patients; patients on tamoxifen should be alerted to report abnormal bleeding.

ASCO guidelines specifically recommend against routine blood counts, liver function tests, and tumor markers (eg, carcinoembryonic antigen), and routine radiologic tests other than mammograms (eg, chest radiographs, bone scans, computed tomography scans, positron emission tomography scans, and breast magnetic resonance imaging tests). Newer data, however, do support the use of surveillance breast magnetic resonance imaging in certain patient subsets (eg, those with BRCA mutations and residual breast tissue).⁶ ASCO provides patient information material that can be helpful to give to patients who have questions about breast cancer surveillance testing.

BOTHERSOME SYMPTOMS

Vasomotor Symptoms Caused by Chemotherapy-related Amenorrhea and Hormonal Therapies

Vasomotor symptoms occur in 65% to 96% of women treated for breast cancer.⁷ In survivors of breast cancer, vasomotor symptoms are often longer lasting and more severe than in the general population. These negatively impact QOL, sleep, and compliance with medications. Breast cancer therapies can cause hot flashes by abruptly interrupting ovarian function (with chemotherapy, ovarian inhibition, and oophorectomy); decreasing estrogen concentrations (aromatase inhibitors [AI]); or decreasing the sensitivity of tissues to estrogen (tamoxifen). Discontinuation of hormone-replacement therapy can also cause problematic symptoms.

Hot flashes are the most common adverse events of adjuvant endocrine therapies, with a prevalence of 50% to 70% in patients treated with tamoxifen.⁸ In this setting, the frequency and severity of hot flashes usually increase during the first 3 months of treatment, after which they plateau. Compared with tamoxifen, the AIs are slightly less likely to cause hot flashes.⁹ In general, the symptoms that result from chemotherapy-induced menopause are more severe than those associated with natural menopause.

Lifestyle options for hot flash relief (eg, keeping the room cold; avoiding spices, caffeine, and hot fluids; using a fan and cooling pillows; and dressing in layers) are sensible and straightforward. Although extremely effective in alleviating hot flashes in 80% to 90% of patients, hormone-replacement therapy is contraindicated in survivors of breast cancer, especially for those with estrogen receptor–positive tumors, because of an increased risk of recurrence.¹⁰

A single intramuscular dose of depomedroxyprogesterone acetate was effective in alleviating hot flashes in 75% to 80% of women with breast cancer, and its effect was long-lasting^{11,12}; however, the safety of this approach has not been clearly delineated.

Efforts to expand the therapeutic options for vasomotor symptoms have led to trials of the following: (1) newer antidepressants, such as selective serotonin reuptake inhibitors paroxetine, sertraline, fluoxetine, citalopram, and escitalopram, and serotonin-norepinephrine reuptake inhibitors venlafaxine and desvenlafaxine; (2) anticonvulsants, such as gabapentin and pregabalin; and (3) the antihypertensive drug clonidine.

Table 1 provides an overview of treatments for hot flashes. Venlafaxine seems no more effective than gabapentin, but was preferred by the patients in an randomized controlled trial (RCT) with a crossover design.¹³ Gabapentin and pregabalin reduce hot flashes in the

general population and survivors of breast cancer.^{14,15} Clonidine had similar effects in survivors of breast cancer treated with tamoxifen.¹⁶

Paroxetine, fluoxetine, and sertraline should be used with caution in patients receiving tamoxifen, because they substantially inhibit CYP 2D6, the enzyme converting tamoxifen to its active metabolite, endoxifen. Venlafaxine, desvenlafaxine, citalopram, and escitalopram seem to inhibit CYP 2D6 to a lesser degree and thus may be better choices in patients receiving tamoxifen.¹⁷

Complementary and alternative methods have been assessed for hot flash treatment, with varying degrees of success. Black cohosh, ginseng, evening primrose oil, wild yam, and phytoestrogens have all been studied prospectively but seem to have minimal, if any, effects.¹⁸ Vitamin E seems to be mildly effective in alleviating hot flashes and can be considered for patients with mild symptoms.¹⁹ Mind-body interventions, such as paced breathing, cognitive behavioral therapy, and yoga, were all suggested to be beneficial in small studies, but systematic reviews revealed methodologic research flaws and, to date, there is no definite proof of benefit.²⁰ It is possible that acupuncture may be helpful for some patients with hot flashes,²¹ but most RCTs of acupuncture versus sham acupuncture have showed no difference between groups.²² Likewise, a review of RCTs on the benefits of physical exercise for treatment of hot flashes was negative.²³ New data support that hypnosis can be beneficial,^{24,25} but additional trials are needed and training is necessary to provide this therapy.

Sexual Dysfunction Caused by Chemotherapy-related Amenorrhea and Hormonal Therapies

Sexuality is an integral part of life and is influenced by physical, psychological, relational, and sociocultural factors.²⁶ Surgery and radiation for breast cancer may alter sexuality by changing body contour and sensation; in addition, early menopause induced by chemotherapy, and hormonal alterations associated with endocrine therapies, can negatively impact the sexual organs. A recent review of sexual dysfunction in female survivors of breast cancer identified a high prevalence of sexual symptoms (30%–100%), the most commonly reported being decreased libido (23%–64%); decreased arousal or lubrication (20%–48%); dyspareunia (35%–38%); anorgasmia (16%–36%); body image concerns (30%–67%); and poor nipple sensation after nipple-sparing mastectomy (>90%).²⁶

Although lumpectomy has been less commonly associated with deterioration in body image compared with mastectomy, sexual functioning seems to be comparable after either surgery,²⁷ regardless of the time since surgery. Women who received chemotherapy are more likely to experience vaginal dryness, dyspareunia, decreased libido, and difficulty achieving orgasm.²⁸ These symptoms are more prevalent in younger women and it seems that chemotherapy-associated sexual dysfunction usually resolves within 10 years after treatment.²⁹

There is strong evidence that treatment with tamoxifen is not associated with sexual dysfunction in most survivors of breast cancer,³⁰ whereas AIs contribute significantly to dissatisfaction with sexual life. In the Anastrozole, Tamoxifen, Alone and in Combination (ATAC) trial, therapy with anastrozole was associated with more vaginal dryness (16% vs 8%), dyspareunia (18% vs 8%), and decreased libido (16% vs 9%) compared with tamoxifen.³¹ Similar findings were shown in a study that examined exemestane versus tamoxifen.³²

There are several barriers to treatment of sexual dysfunction in survivors of breast cancer. First, many medical providers may be uncomfortable discussing sexuality because of

deficiencies in formal training in this field, unfamiliarity with resources for referral, and fear of embarrassing the patient or invading her privacy.^{26,33} Patients may be reluctant to be the first to broach this subject. As such, sexual dysfunction may remain unaddressed in a substantial proportion of survivors of breast cancer despite evidence that, given the opportunity, patients would like to discuss this issue.³⁴

Second, there is no standard tool for detecting sexual dysfunction in survivors of cancer. Recently, it was proposed that the use of the Female Sexual Function Index³⁵ or other patient self-reported assessments be implemented for this purpose.²⁶ A valuable practical approach to assessing cancer-related sexual dysfunction in survivors of cancer, including specific phrases to help opening the discussion, was recently outlined by Bober and Varela.²⁶

Treatment of sexual dysfunction necessitates a comprehensive assessment and intervention that addresses the communication between sexual partners and requires sensitivity to cultural and personal values. The quality of one's relationship is the most consistent predictor of sexual satisfaction in survivors of breast cancer.²⁸

Vaginal lubricants (Astroglide) and moisturizers (Replens, KY Jelly) are effective in alleviating vaginal dryness and dyspareunia.^{36,37} Moisturizers should be used regularly, three to five times a week, to be effective, whereas lubricants are meant to be used as needed (generally before and during sexual activity).

Topical estrogen preparations are more effective than vaginal moisturizers, but their use raises concerns about systemic absorption and possible stimulation of cancer recurrence. Nevertheless, low-dose vaginal estrogens, such as estradiol vaginal ring (Estring), estradiol vaginal tablet (Vagifem), or vaginal conjugated estrogens (Premarin vaginal cream), can be considered for women with significant vaginal symptoms. Systemic absorption of vaginal estrogens is most concerning in women treated with AIs; in these women, vaginal estrogens should be avoided or only used in the short term after thorough counseling regarding potential risks.³⁸ New data support the use of dehydroepiandrosterone as an agent to help vaginal dryness.³⁹ Most of the work has been obtained in patients without prior history of breast cancer. Ongoing work is addressing this issue in patients with a prior history of cancer.

Testosterone does not seem to be beneficial for sexual function in survivors of breast cancer.⁴⁰ The use of vaginal dilators, vibrators, self-stimulating techniques, and pelvic floor relaxation techniques have been advocated for women with vaginal atrophy and stenosis causing vaginal discomfort and dyspareunia.⁴¹ This treatment is best administered in coordination with a mental health specialist, gynecologist, or counselor with expertise in sexual health. Box 1 summarizes the sexual dysfunction issues.

Infertility and Delayed Childbearing Caused by Gonadotoxic and Hormonal Therapies

Young survivors of breast cancer may face delayed child-bearing and infertility because of gonadotoxic chemotherapies and time-consuming hormonal therapies. Chemotherapy damages the ovaries and causes earlier menopause and reduced fertility. The most common chemotherapeutics causing premature ovarian failure are the alkylating agents, followed by platinum agents, anthracyclines, and taxanes.⁴² Conception of a child is strongly discouraged during any cancer systemic or radiation therapy because of potential teratogenicity. Because a standard endocrine therapy course for a premenopausal woman lasts at least 5 years, natural ovarian aging during this period contributes significantly to infertility in many survivors of breast cancer (even those who did not require chemotherapy).

Infertility and worry about possible future infertility are significant burdens for many survivors. The ability to reproduce has been identified as a major concern in this population,⁴³ and not all survivors believe that this issue is adequately addressed by their health care providers.⁴⁴ For new patients with breast cancer that prioritize the ability to bear children in the future, reproductive options can be maximized by early referral to a reproductive endocrinologist. Before the initiation of systemic treatment, embryo and oocyte cryopreservation, and experimental ovarian tissue cryopreservation, may be considered. If a newly diagnosed premenopausal patient has a male partner with whom she would like to conceive, or if she is willing to use sperm from a donor, she may opt for the most widely available and highly effective fertility preservation technique, embryo cryopreservation (ie, retrieval of eggs followed by fertilization, freezing, and storage). If she prefers to store unfertilized eggs because she does not have access to a desirable sperm source, oocyte cryopreservation (ie, retrieval, freezing, and storage of unfertilized eggs) may be best performed at an experienced center. Embryo and oocyte cryopreservation generally require a 2- to 6-week delay in chemotherapy depending on a woman's menstrual calendar, and may theoretically stimulate the growth of hormonally sensitive cancers because of spikes in estradiol and other hormones during stimulation of ovarian follicle development (which optimizes egg retrieval yields). However, new techniques that use letrozole or tamoxifen during ovarian stimulation prevent high spikes in estradiol levels,⁴⁵ and no detrimental impact on prognosis has been associated with this strategy.^{46,47} Ovarian tissue cryopreservation (ie, removal, freezing, and storage of a piece of an ovary) is the most invasive and least well tested of these techniques, but it does not require any hormonal stimulation, and it may minimize delays, because it does not require synchronization with the menstrual cycle.⁴⁸

Even if fertility concerns are not addressed until after breast cancer treatment is completed, prompt reproductive endocrinology referral, as soon as possible, is desirable. Options after breast cancer treatment may include in vitro fertilization, use of donor eggs, and early cessation of hormonal therapy when a patient believes that the benefits outweigh the risks. Use of a decision aid at the time of diagnosis may help reduce regrets about fertility-related decisions later.⁴⁹ Likewise, online reproductive health and fertility education may improve QOL during the survivorship period.⁵⁰

Osteoporosis Caused by Chemotherapy-related Amenorrhea and Antiestrogen Therapies

Osteoporosis, a metabolic disease of the bone characterized by low bone mineral density (BMD) and changes in bone microarchitecture that increase risk of fractures, is a major health issue in survivors of breast cancer, with a prevalence five times higher than in the general population.⁵¹ Estrogen decreases the activity of bone resorptive cells (osteoclasts) and stimulates bone formation by osteoblasts. Age, natural menopause, chemotherapy-induced amenorrhea, ovarian inhibitors, and AIs are all associated with a low estrogenic state. Tamoxifen seems to have detrimental bone resorptive effects in premenopausal women,⁵² but advantageous antiresorptive effects in postmenopausal women.⁵³

Chemotherapy-induced premature menopause is associated with rapid bone loss, comparable with that seen with surgical premature menopause.⁵⁴ Gonadotropin-releasing hormone (GnRH) agonists (eg, goserelin) cause even more bone loss than chemotherapy.⁵⁵ Adjuvant treatment with an AI poses a significantly increased risk of osteoporosis and fractures, although less than that seen with chemotherapy-induced ovarian failure or GnRH agonists.⁴² In a bone substudy within the ATAC trial, women treated with anastrozole experienced a decrease in BMD of 6% at the lumbar spine and 7% at the hip after 5 years of therapy (a tamoxifen and a nonrandomized comparator untreated group had a slight BMD increase and slight BMD decrease, respectively).⁵⁶ At 10 years, there were more fractures in the anastrozole group than in the tamoxifen group (15% vs 11%), a difference accounted for

by fractures during active treatment only, after which there were equal numbers of fractures in the two groups.⁵⁷ Similar findings were reported from studies of adjuvant exemestane and letrozole^{58,59} versus tamoxifen. Of note, women with a normal BMD, before initiation on AI therapy, did not develop osteoporosis during or after completion of AI therapy.

Risks factors for osteoporosis are classified into modifiable (eg, smoking, caffeine intake, inactivity, muscle weakness, low body weight, low calcium and vitamin D intake, low estrogen levels) and nonmodifiable (eg, family history of fractures, white or Asian race, older age, female gender, height, late menarche, hip geometry). However, most fractures in the general population occur in people with a BMD above the osteoporotic range.⁶⁰ The Fracture Assessment Tool (FRAX),⁶¹ which includes modifiable and nonmodifiable risk factors for osteoporosis, may aid assessing an individual's risk of osteoporotic fractures. A 10-year risk of major osteoporotic fractures of greater than or equal to 20% or of hip fracture of greater than or equal to 3%, according to this tool, is considered a clinical indication for bone-strengthening treatment. In women treated with AIs, the FRAX may underestimate the risk of fractures.⁶²

In cancer survivors, ASCO guidelines recommend screening for osteoporosis in high-risk women (age ≥ 65 years; age 60–64 at high risk [family history, previous non-traumatic fracture, weight <70 kg]; those initiating AI therapy; premenopausal women on ovarian suppression), by annual DEXA.⁶³ Other guidelines (National Comprehensive Cancer Network [NCCN], International Expert Panel), recommend screening only for women initiating an AI therapy with DEXA scans every 1 to 2 years.^{62,64} In women with normal BMD at baseline, it is reasonable to repeat testing less frequently. Treatment is recommended for those with a T score less than or equal to -2.5 by the ASCO guidelines, whereas the NCCN recommends treatment for those with a T score less than or equal to -2 or with an FRAX score for which treatment is indicated.

Prevention of bone loss in patients with cancer should start with addressing modifiable risk factors: weight-bearing physical activity; supplemental calcium and vitamin D for a total daily intake (from diet and supplements) of about 1200 mg calcium and 800 IU of vitamin D; smoking cessation; and avoidance of excessive alcohol.⁶³ Vitamin D deficiency is prevalent in survivors of breast cancer, and measurement of serum 25-hydroxyvitamin D levels (followed by replacement for those with deficiency) may be valuable before starting therapy with bone antiresorptive agents.

Bone antiresorptive therapies recommended for survivors of breast cancer belong to two groups of medications: bisphosphonates (alendronate, residronate, ibandronate, pamidronate, and zoledronate) and a monoclonal antibody to receptor activator nuclear factor kappa-B ligands, of which denosumab is the only one clinically available. Both classes work by inhibiting the activity of osteoclasts. Denosumab is Food and Drug Administration (FDA) approved for use in postmenopausal osteoporosis, women with osteopenia on AI, and women with breast cancer metastatic to the bone. In osteopenic survivors of breast cancer treated with an AI, denosumab (60 mg subcutaneously every 6 months) increased the lumbar spine BMD by 7.6% at 2 years, compared with placebo.⁶⁵

Although starting bisphosphonates at the time of initiation of chemotherapy significantly increases BMD compared with a delayed approach or to a placebo arm,^{65,66} this approach lacks long-term follow-up and data proving fewer bone fractures. Recent meta-analyses failed to reveal benefit from up-front versus delayed use of bisphosphonates in women initiating AI therapy, with regard to fractures or survival.⁶⁷ Because of concerns about osteonecrosis of the jaw, atypical femoral neck fractures, and esophageal cancer associated with the use of bisphosphonates, the FDA has recommended that the benefits and risks of

this therapy be assessed periodically and therapy be discontinued if the risk of fractures has subsided.⁶⁸ Box 2 provides a synopsis of this topic.

Musculoskeletal Complaints Related to AIs

AIs were used in clinical practice for some time before it was widely recognized that they caused arthralgias. One of the earliest clinical trials demonstrating increased risk of musculoskeletal symptoms was the ATAC trial, which reported a 30% incidence of musculoskeletal disorders with anastrozole versus a 24% incidence with tamoxifen.⁶⁹ This statistically significant difference likely underestimated the true incidence of this problem because it required clinician documentation of a clinical problem that had not been identified to possibly be associated with AIs, as opposed to measuring patient-reported symptoms that queried about this toxicity. Because this was not a widely recognized problem at the time, clinicians were likely not attuned to it.

Despite the current paucity of placebo-controlled data regarding patient-reported arthralgias on AIs, these medications seem to cause musculoskeletal symptoms in approximately 50% of patients, with 15% of patients experiencing severe symptoms.⁷⁰ Hands and knees are often involved. A few patients develop symptoms within weeks to a month, whereas others first notice symptoms a year or more after drug initiation. The incidence of AI-mediated musculoskeletal symptoms seems to be relatively similar among the three clinically available AIs: (1) anastrozole, (2) letrozole, and (3) exemestane. Joint abnormalities can be seen radiologically in some affected patients.⁷¹

Although the cause of AI-mediated musculoskeletal symptoms has not been definitively determined, the most likely cause is from estrogen deficiency. In 1925, Cecil and Archer first described “arthritis of the menopause” as the rapid development of hand and knee osteoarthritis after the cessation of menses.

Currently, there are no proved drugs or procedures for patients suffering AI-mediated arthralgias. In clinical practice, nonsteroidal anti-inflammatory medications do seem to help many patients. Phase III clinical trials are planned or ongoing for testosterone, vitamin D, acupuncture, and an omega-3 fatty acid. At this time, the recommended treatment of patients with severe AI arthralgias is to temporarily discontinue the drug. In most cases, symptoms largely resolve within a month or so. At that time, another AI may be tried. Some patients tolerate this better, whereas other patients develop recurrent symptoms. Another option is to switch antiestrogen therapy to tamoxifen. For patients with minimal benefits from antiestrogen therapy (eg, an 80-year-old woman with a 0.5 cm breast cancer) consideration of stopping adjuvant hormonal therapy may be appropriate.

Weight Gain

Weight gain is common in patients with breast cancer treated with chemotherapy (average gain is 2.5–6.2 kg, but is more in premenopausal women and those treated with multiagent regimens),⁷² but not usually in patients treated with endocrine therapy alone, compared with placebo.⁷³ Chemotherapy causes sarcopenic obesity, characterized by loss of lean mass and gain of fat mass. Decreased physical activity caused by fatigue, decreased resting energy expenditure, and, to lesser degree, overeating, have been shown to contribute to obesity after chemotherapy.⁷⁴ Weight gain after breast cancer diagnosis is associated with a decreased QOL and an increased risk of cardiovascular disease, diabetes, orthopedic complications, and gallbladder disease. Weight gain might increase breast cancer–specific and overall mortality, although this has not been consistently established.⁷⁵

It remains unclear whether purposeful weight loss after breast cancer treatment impacts breast cancer outcomes. There is strong evidence that implementing a physical exercise

program after breast cancer treatment is associated with a decreased risk of cancer recurrence and death, but the mechanism for this is unclear. Large studies of dietary interventions in early survivors of breast cancer have reported a positive effect on disease-free survival only if the intervention was associated with weight loss.⁷⁶ Small studies showed success with weight loss through multimodality interventions that included caloric restriction, exercise, and psychologic support.⁷⁷ Larger studies are underway to analyze the impact of multimodality approaches on weight loss and survival.

Currently, the American College of Sports Medicine⁷⁸ and the American Cancer Society⁷⁹ recommend moderate-intensity aerobic activity for greater than or equal to 150 minutes per week; strength training at least 2 days per week; a diet rich in fruits, vegetables, and whole grains; and limiting the ingestion of processed foods, to achieve or maintain a healthy weight.

Cognitive Changes

Cognitive impairment associated with cancer treatments includes problems with attention, concentration, executive function, and working memory. Cross-sectional studies report a high prevalence of cognitive impairment, between 15% and 75%. In some studies that measure pretreatment cognitive functioning, 15% to 25% of patients with breast cancer had worse cognitive function after chemotherapy,⁸⁰ whereas other recent studies have been negative.⁸¹ Heterogeneity of the measured outcomes and patient populations, and sometimes a lack of pretreatment cognitive assessment, may account for these conflicting results.

Interestingly, 20% to 30% of patients with breast cancer had a lower than expected cognitive performance before treatment, irrespective of any psychological factors, such as depression, anxiety, fatigue, or anesthesia type. It is postulated that cancer can induce an inflammatory state that induces cognitive dysfunction or that cancer and cognition might have a common risk factor.⁸² Cognitive changes after breast cancer treatment were initially attributed wholly to chemotherapy, but evidence is emerging to suggest a role for endocrine therapy. Tamoxifen seems to negatively affect cognitive abilities, whereas AIs do not.⁸³

Older patients and those with a lower cognitive reserve are more vulnerable to treatment-induced cognitive deficits.⁸⁴ Genetic factors involved in apolipoprotein E and catechol *O*-methyltransferase metabolism may also contribute to predisposition toward chemotherapy-induced cognitive decline.⁸⁵

Treatment of cognitive dysfunction has been poorly studied. The natural history seems to be one of slow recovery and return to pretreatment levels in about 6 months. Modafinil and cognitive behavioral training have been studied and found to be promising.^{86,87}

Fatigue

Cancer-related fatigue (CRF) is a persistent feeling of emotional, physical, and cognitive exhaustion associated with cancer diagnosis or treatment, out of proportion to recent activity and not relieved by rest.⁸⁸ CRF is often identified as the most distressing side effect of cancer diagnosis and treatments. CRF significantly impacts overall QOL and patients consider fatigue to be a major disruptor of daily activities. However, health care providers rarely assess for presence and severity of fatigue, and often attribute less importance to fatigue than do patients.⁸⁹ The pathophysiology of fatigue in this population is complex and poorly understood; proposed mechanisms include neurotoxicity of cancer treatments, chronic stress affecting the hypothalamic-pituitary-adrenal axis, systemic inflammatory response, hormonal changes of menopause, anemia, and immune activation.⁹⁰

The prevalence of CRF varies significantly, based on the diagnostic criteria used, and has been reported to be between 15% and 90%.⁹¹ In one study, 21% were found to report persistent fatigue beyond 5 years.⁹²

NCCN guidelines recommend fatigue assessments at initial visit, during chemotherapy, and when advanced cancer is diagnosed.⁸⁸ The recommended screening tool is a visual analog scale (How would you rate your fatigue from 0–10?) with scores between 1–3, 4–6, and 7–10 representing mild, moderate, and severe fatigue, respectively.

Certain breast cancer treatments are linked to fatigue. Radiation is associated with fatigue that is usually worst late in the course, and persistent fatigue. A psychological mechanism has been proposed, but not proved, for survivors of early stage breast cancer receiving radiation. Receiving both chemotherapy and radiation is known to be associated with a greater risk of CRF than either therapy alone.⁹²

Managing fatigue should include, at a minimum, instruction on energy conservation for those with severe symptoms, and treatment of comorbid conditions (eg, insomnia, pain, depression, anemia, cardiomyopathy [CMP], and hypothyroidism).⁹³ However, improvement in depression or insomnia with pharmacologic interventions has not been found to be associated with decreased fatigue,⁹⁴ although bupropion is still under study. Aerobic physical exercise during or after completion of breast cancer treatments was found to reduce fatigue in a recent meta-analysis that included 56 studies (28 of survivors of breast cancer), whereas resistive (eg, strength training) and alternative exercise (eg, yoga and qigong) methods were not found to be helpful.⁹⁵ To date, most of the literature does not support that psychostimulants (eg, methylphenidate, modafinil) are very helpful in patients with CRF.

American ginseng did improve the general and physical subscales of fatigue in a double-blind RCT, but not the mental, emotional, and vigor dimensions of fatigue.⁹⁶ One small study suggested that guarana, a stimulant from the seeds of an Amazonian plant, improved fatigue, but this needs to be confirmed in larger studies. Box 3 provides a summary of this topic.

Neuropathy

Although many chemotherapy drugs can cause bothersome neuropathy, taxanes are the most common culprits in patients with breast cancer. This section focuses on paclitaxel-induced neuropathy, because the best natural history information is available with this drug, although docetaxel also causes neuropathy to a slightly lesser degree.⁹⁷ Despite previous claims, nab-paclitaxel seems to cause as much neuropathy, if not more, than standard paclitaxel.⁹⁸

It was recognized in early clinical trials that paclitaxel caused an acute pain syndrome, which was uncommon with previous chemotherapeutic agents, occurring within days of each dose and largely abating after a few to several days. This pain syndrome became commonly known as “paclitaxel-induced arthralgia/myalgia.” In recent years, it has been hypothesized that this pain syndrome is not related to joint or muscle pathology, but is more likely a type of neuropathy.^{99,100} In addition to the acute pain syndrome, paclitaxel commonly causes a distal peripheral neuropathy, which commonly presents in a stocking-glove distribution. It is primarily a sensory neuropathy, but some patients have motor or autonomic neuropathy components. This neuropathy, which is the most common dose-limiting toxicity of this drug, commonly occurs over the first several weeks or few months of therapy. Although the symptoms usually lessen after discontinuation of paclitaxel, neuropathy can be persistent and severe for an appreciable subset of patients, and can cause

long-term disability. At this time, there is no proved antidote to prevent paclitaxel-induced neuropathy other than dose reduction or discontinuation.

For patients with established paclitaxel-induced neuropathy, there is a dearth of proved effective therapies. Gabapentinoids, such as gabapentin and pregabalin, are commonly used clinically, but a randomized, placebo-controlled, double-blinded clinical trial failed to support this therapy.¹⁰¹ Duloxetine,¹⁰² Scrambler therapy,¹⁰³ a topical preparation of baclofen/amitriptyline/ketamine,¹⁰⁴ and topical menthol have all shown some promise.¹⁰⁵

Cardiac Toxicity

Radiation therapy, chemotherapy, and endocrine therapy have all been incriminated in cardiotoxicity during treatment of breast cancer. Anthracycline-based chemotherapeutic regimens have been in use since the 1980s, and their cardiotoxicity is well recognized.¹⁰⁶ They can cause a dose-dependent CMP resulting in chronic heart failure. The mechanism by which anthracyclines cause CMP is believed to be a direct toxic effect on the myocytes with generation of free radicals. This syndrome can clinically manifest immediately after administration or after a delay of months or years.¹⁰⁶ Traditionally, it was believed that this heart damage is irreversible (type I cardiac toxicity) and poorly responsive to treatment; however, newer studies have shown that early intervention with angiotensin-converting enzyme inhibitors (ACEI) or β -blockers leads to complete left ventricular ejection fraction recovery.¹⁰⁷

The incidence of clinical CMP reaches 5% with cumulative doxorubicin and epirubicin doses of 400 mg/m² and 920 mg/m², respectively.¹⁰⁸ Modern trials, in which the cumulative dose of doxorubicin is much lower (in the range of 240 mg/m²) have reported a CMP incidence of 0% to 1.6%, and up to 2.1% if taxanes are added.¹⁰⁹ However, the incidence of subclinical heart failure identified through echocardiograms or Multi Gated Acquisition (MUGA) scans is much higher, up to 23% for grade 1 or 2 cardiac toxicity.¹¹⁰ Factors associated with an increased risk of anthracycline-induced CMP include older age, hypertension, preexisting coronary artery disease, and previous mediastinal radiotherapy.¹⁰⁶

Data on the natural history of anthracycline-induced CMP are scarce and based mainly on retrospective analyses. One study reported a poor prognosis, compared with other more common causes of CMP, and a 60% 2-year mortality.¹¹¹ Newer prospective studies have shown that, if detected early, CMP is treatable and frequently curable with the use of an ACEI or β -blockade.¹⁰⁷ The diagnosis of CMP during chemotherapy may be problematic if it results in a dose decrease, delay, or cessation of further anthracycline treatments, potentially impairing cancer outcomes.

Weekly dosing or prolonged infusion (rather than the standard dosing every 3 weeks) may be considered in patients with the previously mentioned risk factors for possible prevention of anthracycline-induced CMP.^{112,113} Pegylated liposomal doxorubicin is less cardiotoxic, but potentially less effective than the parent compound.¹¹⁴ Dexrazoxane is a cardioprotective medication that was proved to significantly decrease the risk of heart failure and cardiac events during and after treatment with anthracyclines.¹¹⁵ However, it is FDA approved for use only in patients who require additional doses of anthracyclines after having already received 300 mg/m², and consequently it is rarely used. Short-term data on taxanes does not suggest that they increase risk of anthracycline-induced cardiotoxicity.

HER-2 neu-directed therapies are associated with symptomatic cardiac dysfunction in 2% to 4% of patients, whereas 3% to 18% develop asymptomatic CMP, usually reversible with the discontinuation of the drug (type II cardiac dysfunction).¹¹⁶ Cardiotoxicity is rare in patients

who have not received anthracyclines before trastuzumab.¹¹⁷ Antiangiogenic-based chemotherapy may also cause cardiotoxicity by uncontrolled hypertension.¹¹⁸

Radiation therapy, at least by protocols used until the mid-1980s, is associated with an increased risk of dying of cardiac disease and vascular disease; a higher risk has been seen with radiation to the left breast or left chest wall and particularly to the internal mammary chain on either side. The risk increases with the time from radiation and is higher among smokers.¹¹⁹ Newer radiation techniques deliver a lower dose of cardiac radiation, although parts of the heart and the left anterior descending artery likely continue to receive concerning amounts of radiation.¹²⁰ Aggressive treatment of any cardiovascular risk factors is of paramount importance in survivors of breast cancer treated with radiation therapy, especially if left-sided.

Tamoxifen has not been associated with cardiotoxicity, but a recent meta-analysis has demonstrated excess cardiac mortality in women treated with AI for 5 years versus tamoxifen or versus tamoxifen followed by AI for 2 to 3 years.¹²¹

Early detection of CMP may allow avoidance of irreversible damage¹²² but there are no clear guidelines for detection of subclinical CMP. Serial electrocardiograms, echocardiograms, or MUGA scans have been suggested, but these have low sensitivity and specificity in this setting. Troponin I and B-type natriuretic peptide (BNP) are emerging as potential predictive markers for the development of anthracycline-induced CMP and as barometers of response to therapy for this problem.¹²³ Currently, no cardiac screening is recommended for the average breast cancer survivor. Treatment of asymptomatic or symptomatic CMP should include ACEI or β -blocker, aggressive control of blood pressure, and other cardiovascular risk factors.

TREATMENT-RELATED CANCERS

Patients who receive radiation or chemotherapy for breast cancer may develop therapy-related myelodysplastic syndrome or leukemia. Rates of chronic myelogenous leukemia, acute lymphocytic leukemia, and acute myelogenous leukemia (AML) have all been found to be increased by chemotherapy,¹²⁴⁻¹²⁶ with alkylating agents, topoisomerase II inhibitors (associated with 11q23 chromosomal alterations), and platinum compounds all implicated.¹²⁷ Out of 16,705 French survivors of breast cancer treated at a single center between 1981 and 1997, at a median follow-up of 10.5 years, 709 patients had developed a second malignancy.¹²⁸ Compared with registry data from the general French population, the standardized incidence rate of leukemia was 2.07, and the receipt of chemotherapy was strongly associated with this increased risk. Similarly, in the Danish Cancer Registry, for patients with breast cancer registered between 1977 and 2001, the standardized incidence ratio for acute leukemia was 2.02 compared with the general population.¹²⁹ Likewise, an analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results database showed that AML was diagnosed in the 10 years after the breast cancer diagnosis in 1.8% of women who had received chemotherapy and 1.2% of those who had not.¹²⁶ In a later Surveillance, Epidemiology, and End Results analysis of more female survivors of breast cancer, there was an age-dependent elevated risk of later developing AML in women younger than 50 years old (relative risk, 4.14; $P < .001$) and 50 to 64 years old (relative risk, 2.19; $P < .001$), but not in those 65 and older (relative risk, 1.19; $P = .123$) when compared with the expected incidence of AML. Higher stage was associated with an elevated risk of AML (likely caused by a greater likelihood of receiving chemotherapy and radiation with stage III vs stage I disease), and this association was strongest in the youngest women.¹³⁰ It is uncertain whether growth factors that support white blood cell counts during chemotherapy contribute to these risks.^{126,131}

Alkylating chemotherapy and, more substantially, radiation, can also cause lung cancers, sarcomas, and other solid tumors.¹²⁷ In the Danish Cancer Registry, the relative risk of lung cancer in patients who received radiation for breast cancer, compared with those who had not, was 1.33 (95% confidence interval, 1.00–1.77).¹²⁹

Tamoxifen increases the risk of uterine cancer. In the Danish Cancer Registry, patients with breast cancer who received tamoxifen had a standardized incidence ratio for uterine cancer of 1.83, whereas patients with breast cancer who did not receive tamoxifen only had a standardized incidence ratio of 1.04.¹²⁹

Nevertheless, because of low prevalence of secondary malignancies, the NCCN recommends against routine complete blood counts, blood work, or imaging tests to evaluate for new nonbreast malignancies in survivors of breast cancer in general.¹³² Patients on tamoxifen are advised to undergo a gynecologic examination annually to monitor for endometrial malignancy. In patients who are known to carry a genetic mutation (eg, p53) that predisposes to a higher risk of a specific malignancy, decisions about screening should be individualized.

ORGANIZING FOLLOW-UP CARE

In recent years, attention to coordinated follow-up for survivors of breast cancer has grown. The Institute of Medicine identified this as a priority for survivors of all cancers.¹³³ An effort is underway to communicate better to patients and providers about the specifics of the cancer diagnosis and the oncologic care received, such that future care can be better tailored to each survivor's needs. Treatment summaries synopses an individual's cancer type; stage; methods and doses (where appropriate) of treatment; and toxicities experienced to date. Survivorship care plans lay out a recommended approach to future care, usually including optimal visit frequency and frequency of screening for recurrences, new primaries, and other medical problems.

These treatment summaries and survivorship care plans aim to improve patient understanding and to encourage communication and coordination among primary care providers, oncologists, and other providers (eg, gynecologists, cardiologists, surgeons, and so forth). Ideally, better coordination will help minimize redundant care (ie, repetitive testing and unnecessary visits). Given that health care resources are limited, it is hoped that these efforts streamline follow-up procedures and facilitate efficient and high-quality survivorship care. However, one recent study failed to show a significant benefit to administration of survivorship care plans to patients with breast cancer as part of a 30-minute visit with a nurse practitioner at the completion of curative therapy.¹³⁴ Nevertheless, broader implementation of survivorship care coordination for cancer survivors is of great interest to many patients and providers.¹³⁵

SUMMARY

Survivors of breast cancer are confronted with a plethora of cancer treatment-related long-term symptoms, the most common being fatigue, hot flashes, sexual dysfunction, arthralgias, neuropathy, and cognitive dysfunction. Survivors of breast cancer also face cancer treatment-related disease states, such as osteoporosis, cardiac dysfunction, obesity, infertility, and secondary cancers. Evidence-based recommendations for screening, prevention, and early intervention should be implemented to improve QOL and decrease comorbidities in this population.

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Box 1**Sexual dysfunction key points**

- The most common sexual symptoms in survivors of breast cancer are (1) decreased libido, arousal, or lubrication; (2) dyspareunia; (3) anorgasm; (4) body image concerns; and (5) decreased nipple sensation
- Sexual dysfunction does not seem to differ substantially after lumpectomy versus mastectomy
- Chemotherapy and AI therapy, but not tamoxifen, are associated with an increased risk of sexual dysfunction
- It is the responsibility of the provider to open the discussion on sexual dysfunction
- Screening for sexual dysfunction should be performed regularly through objective or self-reported assessment tools
- Hormone-replacement therapy is contraindicated for treatment of sexual dysfunction in survivors of breast cancer
- Testosterone without estrogen does not seem to be helpful in treating sexual dysfunction in female survivors
- Vaginal moisturizers (Replens, KY Jelly) and lubricants (Astroglide) are effective for dyspareunia and vaginal dryness, and should be used as a first-line therapy
- Low-dose vaginal estrogen preparations (Vagifem, Estring, Premarin cream) may be considered for selected women with severe vaginal dryness
- Vaginal dilators, vibrators, self-stimulation, and pelvic relaxation techniques may ameliorate vaginal stenosis and severe dyspareunia
- Referral to mental health specialists, sexual counselors, and gynecologists may be considered for women with severe symptoms

Box 2**Osteoporosis key points**

- Treatment with AI, GnRH, or chemotherapy poses a significant risk of osteoporosis
- Tamoxifen has a slight bone resorptive effect on BMD in premenopausal women, but has bone protective effects after menopause
- Screening for osteoporosis with DEXA scans every 1 to 2 years is recommended in survivors of breast cancer greater than or equal to 65 years of age, age 60 to 64 at high risk, initiating AI therapy, or premenopausal on ovarian suppression
- Prevention of bone loss can be achieved through weight-bearing physical activity, supplemental calcium and vitamin D, smoking cessation, and avoidance of excessive alcohol intake
- Treatment of osteoporosis is recommended for women with a T score less than or equal to -2.5 or a T score less than or equal to -2 and a high FRAX score (20% risk of major osteoporotic fracture or 3% risk of hip fracture)
- Bisphosphonates (pamidronate, residronate, and zoledronic acid) or denosumab (receptor activator nuclear factor kappa-B ligands inhibitor) can treat or prevent osteoporosis in survivors of breast cancer
- There is no evidence that up-front versus delayed treatment with these medication improves clinically relevant bone outcomes

Box 3**Fatigue key points**

- Fatigue is one of the most distressing cancer-related symptoms and significantly impacts QOL
- Screening for fatigue with a simple visual analog scale is recommended at initial visit, during chemotherapy, and at recurrence
- In patients with fatigue, one must evaluate for anemia, hypothyroidism, and CMP
- Depression and insomnia often coexist with fatigue, and should be treated
- Treatment of fatigue should include energy-conservation measures for those with severe symptoms and aerobic exercise during and after treatment for those able to exercise

KEY POINTS

- Surveillance after early stage breast cancer should include routine mammograms, physical examinations, and histories, but not blood work or imaging focused on possible distant sites of relapse.
- Vasomotor symptoms, sexual dysfunction, infertility, osteoporosis, musculoskeletal pain, weight gain, cognitive changes, fatigue, neuropathy, congestive heart failure, and treatment-related cancers can all plague survivors of breast cancer.
- Efforts are underway to coordinate follow-up care for survivors of breast cancer and to optimize management of the physical, mental, and emotional sequelae of breast cancer and breast cancer treatment.

Table 1
Effectiveness of different interventions for hot flashes

Agent	Dose	% of Patients in Active Arm with 50% Decrease in Baseline Hot Flash Score ^{136,137}	% of Patients in Placebo Arm with 50% Decrease in Baseline Hot Flash Score ^{136,137}	Other Outcomes More Common in Active Arm vs Placebo
MPA ¹³⁸	400 mg intramuscularly	72	Comparison with venlafaxine	No placebo data
Megestrol acetate ¹²	20 mg BID	63	30	Withdrawal menstrual bleeding
Venlafaxine ¹³⁹	37.5 mg/d	54	30	Nausea, appetite loss, dizziness, constipation, dry mouth, sleepiness, improved quality of life
Venlafaxine ¹³⁹	75 mg/d	70		
Venlafaxine ¹³⁹	150 mg/d	62		
Fluoxetine ¹⁴⁰	20 mg/d	70	52	None
Paroxetine CR ¹⁴¹	12.5 mg/d	50	49	None
Paroxetine CR ¹⁴¹	25 mg/d	68		None
Paroxetine ¹⁴²	10 mg/d	70	33; 57 ^a	No side effects. Improved sleep
Paroxetine ¹⁴²	20 mg/d	76		Nausea
Sertraline ¹⁴³⁻¹⁴⁴	50 mg/d	40–50	21–38	Nausea, fatigue, diarrhea, anxiety
Sertraline ¹⁴⁵	100 mg/d	56	41	Nausea
Gabapentin ¹⁴	300 mg/d	46	27	Decrease in appetite, decrease in pain
Gabapentin ^{14,146}	900 mg/d	56–63	27–38	
Gabapentin ¹⁴⁷	2400 mg/d	84	47	Trend toward more headache, dizziness, disorientation, sleep disturbance
Clonidine ¹⁶	0.1 mg/d oral or patch	37	30	Difficulty sleeping, dry mouth, constipation, skin rash from patch, improved quality of life
Vitamin E ¹⁴⁸	800 IU/d	32	30	None
Soy ¹⁴⁹	70–150 mg isoflavones/d	30	?	None
Black cohosh ¹⁵⁰	20 mg/d	20	30	None

All agents were compared with placebo unless otherwise noted.

Data from Loprinzi CL, Barton DL, Sloan JA, et al. Mayo Clinic and North Central Cancer Treatment Group hot flash studies: a 20-year experience. *Menopause* 2008;15(4 Pt 1):655–60; and Loprinzi CL, Sloan J, Stearns V, et al. Newer antidepressants and gabapentin for hot flashes: an individual patient pooled analysis. *J Clin Oncol* 2009;27(17):2831–7.

^aThis study had two placebo arms.