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Management of Potential Long-Term Toxicities in Breast Cancer Patients

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Abstract

Breast cancer is the most common non-cutaneous malignancy among women, and there are over 3 million breast cancer survivors living in the United States today. Excellent cure rates with modern therapies are associated with substantial toxicities for many women; it is important that health care providers attend to the resulting symptoms and issues to optimize quality of life in this population. In this article, we review management options for potential long term toxicities in breast cancer survivors, with a particular focus on bone health, fertility preservation, premature menopause, cardiac **dysfunction**, and cognitive impairment.

Keywords

cardiomyopathy; fertility; cognitive function; menopause; breast neoplasm; osteoporosis; *breast cancer, toxicities, potential long term toxicities, quality of life, review.*

Introduction

In 2016, it is estimated that there are approximately 3.1 million breast cancer survivors in the United States (1). Breast cancer is the most common non-cutaneous malignancy among women, and 5-year survival rates after treatment with curative intent are approximately 90% (2). These patients have unique medical considerations, which include the potential for cardiotoxicity related to prior treatment with anthracycline or trastuzumab, menopausal symptoms, cognitive dysfunction, and impaired bone health. In premenopausal women, the risk of loss of fertility and premature menopause should be appropriately addressed prior to initiation of breast cancer treatment. Medical oncologists and primary care providers must be adept in the management of these issues in order to provide breast cancer survivors with practical, social, and psychological support. In this article, we describe optimal care for this patient population.

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Compliance with Ethics Guidelines

Conflict of Interest

Ciara C. O'Sullivan and Kathryn J. Ruddy declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

BONE HEALTH

Approximately two-thirds of breast cancers express estrogen and/or progesterone receptors (3). Therefore, treatments aimed at inhibiting estrogen signaling in cancer cells are fundamental in patient management. In postmenopausal women, third generation aromatase inhibitors (AIs) have superseded tamoxifen in improving disease-free survival (DFS) at the expense of reduced bone mineral density and increased fracture risk (4), which in turn negatively impacts quality of life(5). Tamoxifen can cause a significant reduction in bone mineral density in premenopausal women, but prevents bone loss in postmenopausal women (6). Bone directed therapies are associated with the prevention of AI-induced bone loss and a reduction in fracture risk(7). Additionally, recent data suggest that adjuvant bisphosphonate treatment may reduce the incidence of osseous metastases in postmenopausal breast cancer patients (8). Consequently, oncologists have become more involved in the diagnosis and management of treatment-related osteopenia and osteoporosis in recent years.

Common bone-directed therapies are classified into two groups: bisphosphonates (e.g. zoledronic acid, pamidronate) and RANK ligand inhibitors (denosumab). The Z-FAST (9), ZO-FAST (10), and ABSCG-12(11) studies demonstrated that the addition of bone-directed treatment to cancer treatment prevented an iatrogenic reduction in bone mineral density in early stage breast cancer patients who were either post-menopausal or receiving ovarian function suppression. However, the role of adjuvant bisphosphonate therapy, in addition to the optimal dose and scheduling, has not been clearly defined in this setting due to conflicting results from several large clinical trials with long term follow up (10–12). Results from a large meta-analysis of over 20,000 women demonstrated that the use of adjuvant bisphosphates in postmenopausal breast cancer patients (including women >55 years if menopausal status was not known) reduced the risk of osseous metastases by 34 % ($p = .00001$) and the risk of breast cancer related death by 17 % ($p = .004$) (8).

In the phase III ABSCG-18 study, postmenopausal women with early stage breast cancer were randomized to treatment with denosumab or placebo during AI therapy (13). Early results from this study showed a halving of the fracture rate among postmenopausal women with hormone-receptor (HR)-positive breast cancer on AIs who were treated with adjuvant denosumab vs. placebo (14). More recently, an intention-to-treat analysis showed that denosumab also improved DFS (a secondary outcome in this study) with borderline statistical significance (hazard ratio 0.82; 95 % CI, 0.66 – 1.0). The absolute magnitude of benefit was approximately 3 % after 7 years follow up; further subset analyses inferred that this benefit was greatest in women with large, infiltrating ductal carcinomas as well as when denosumab was started early in conjunction with AI therapy. In summary, the DFS benefit observed with adjuvant denosumab in this study was similar to that observed in the meta-analyses of use of bisphosphonate therapy in this setting.

Guidelines are available to assist oncologists in maintaining bone health during adjuvant endocrine therapy for breast cancer (15). General recommendations include calcium and vitamin D supplementation and the modification of risk factors such smoking, physical inactivity and alcohol use.

A large European consensus panel recently recommended that bisphosphonates be considered standard of care for the prevention of cancer treatment-induced bone loss in all patients with a T score of < -2.0 or ≥ 2 clinical risk factors for fracture (16). The panel also suggested that bisphosphonates (either intravenous zoledronic acid or oral clodronate) should be considered part of adjuvant breast cancer treatment for post-menopausal women and those receiving ovarian function suppression, and the risks and benefits should be discussed accordingly. In this setting, zoledronic acid is generally administered at a dose of 4mg every six months over three years (17).

While dual energy x-ray absorptiometry (DEXA) scans can be helpful in the diagnosis of osteopenia or osteoporosis in breast cancer survivors, bone mineral density should not be the sole determinant of initiation of bone strengthening medication (18). The Fracture Risk Assessment Tool (FRAX) is a risk prediction model that estimates the 10-year probability of major osteoporotic fractures and includes clinical factors and ethnicity; however, this tool may underestimate fracture risk in some breast cancer survivors (19). Neither a baseline DEXA nor a FRAX estimate is necessary for consideration of bone modifying therapy if a person's breast cancer recurrence risk is high enough to warrant bisphosphonate or denosumab therapy regardless of the result.

INFERTILITY

Breast cancer is the most common malignancy in women of childbearing age (20). Due to the recent societal trend for women to postpone childbearing for practical, professional, and cultural reasons (21), an increasing number of newly diagnosed breast cancer patients have either not started or not completed their families and have significant concerns regarding treatment-related infertility (22). Because breast cancer in younger women frequently has aggressive biological features, gonadotoxic systemic chemotherapy is often recommended. The risk of chemotherapy-related infertility is closely associated with the age of the patient at the time of treatment and the type of chemotherapy administered (alkylating agents such as cyclophosphamide are especially gonadotoxic) (23). In an analysis of three prospective trials in which patients were treated with doxorubicin-based regimens, the rates of chemotherapy-induced amenorrhea (CIA) were 0 %, 33 % and 96 %, respectively, in women aged <30 , 30–39 and 40–49. Menses resumed in approximately 50 % of amenorrheic women aged ≤ 39 , but in only a minority of women aged ≥ 40 (24). Additionally, recent data demonstrated benefit for extended adjuvant endocrine therapy for women with hormone-receptor positive breast cancer (though the vast majority of patients in these trials were postmenopausal women) (25). Longer courses of endocrine therapy will postpone childbearing, allowing more natural decline in ovarian reserve with age. The ongoing POSITIVE trial will assess the safety of interrupting adjuvant endocrine therapy in this setting to allow for the use of assisted reproductive techniques and pregnancy.

Fertility preservation techniques—Fortunately, assisted reproductive techniques do appear to be safe for patients with newly diagnosed breast cancer (26, 27). There are several options for fertility preservation in breast cancer patients (28). The most established method is embryo cryopreservation, which entails controlled ovarian stimulation using exogenous hormones to promote maturation of ovarian follicles, followed by in vitro fertilization (IVF)

and embryo freezing (29). This option is recommended for partnered women or women willing to use a sperm donor who have adequate time to undergo the procedure. Given the recent increase in live birth rates after unfertilized egg freezing (30), oocyte cryopreservation was recently declared as an alternative standard option for fertility preservation by the American Society for Reproductive Medicine (22); this procedure is similar to embryo cryopreservation except that oocytes are frozen prior to fertilization. Because ovarian stimulating drugs induce estrogen levels that are approximately ten-fold greater than normal, theoretically increasing the chance of breast cancer recurrence (31), the use of alternative ovarian stimulation protocols, e.g. follicle-stimulating hormone (FSH) and letrozole, or FSH and tamoxifen, is popular for this patient population (32, 33). While oocytes may be aspirated without hormonal stimulation, the yield with this technique is much lower (34). Of note, pregnancy outcomes in breast cancer survivors who underwent ovarian stimulation with letrozole and gonadotropins are comparable to those in women who do not have a cancer diagnosis, e.g. a fertility preservation rate of 51.5 % in 33 women who attempted pregnancy using cryopreserved embryos (35). GnRH analogues may also be used for fertility preservation. Although data from large meta-analyses are conflicting, two breast cancer-specific randomized controlled trials both showed a significantly lower rate of post-chemotherapy ovarian failure in patients treated with chemotherapy and a GnRH analogue versus chemotherapy alone (36, 37).

Obstacles to fertility preservation may include limited knowledge regarding available options, lack of timely referral to reproductive endocrinology, concerns regarding treatment delay and disease recurrence, and financial and emotional issues (38–41). Given the potential for cancer treatment-related infertility to adversely affect quality of life in breast cancer survivors, it is imperative that eligible patients of childbearing age are provided with information regarding fertility preservation in a structured and timely fashion. Unfortunately, there are sometimes delays or omissions in referral of suitable patients to reproductive endocrinology (42, 43). The majority of comprehensive cancer centers do not have standard algorithms in place to refer cancer patients of childbearing age to reproductive endocrinology (44). In addition, many women referred to reproductive endocrinology do not pursue assisted reproductive techniques (only 7.6 % of referred patients in a large European study) (45). The 2013 American Society of Oncology (ASCO) guidelines recommend that the first care provider who interacts with a newly diagnosed breast cancer patient of childbearing age should assess the patient's fertility goals and provide the relevant information prior to initiating cancer-directed therapy (22). Barriers that prevent oncologists from discussing options for fertility preservation include lack of knowledge and time, perceived high cost, emotional discomfort, insurance issues, and concerns regarding patient prognosis (46, 47). Importantly, some insurance companies are now extending coverage to allow cancer patients to access fertility services (48). Although evidence suggests that pregnancy after a breast cancer diagnosis is safe (49), some oncologists and patients have concerns regarding the safety of future pregnancy. These barriers to fertility preservation likely contribute to the fact that the likelihood of a first pregnancy is halved after a cancer diagnosis (50).

Causes of menopausal symptoms—Hot flashes and vaginal dryness are common in women who undergo an early menopause due to chemotherapy (51), as well as in recipients of endocrine therapy. Both symptoms can impair overall quality of life, and vaginal dryness can limit sexual functioning (52, 53). Management strategies generally avoid systemic hormonal supplementation based on data from the Hormonal Replacement Therapy after Breast Cancer Diagnosis—Is it Safe? (HABITS) trial showing that two years of estrogen-based treatment of menopausal symptoms increased the risk of recurrence 3-fold in breast cancer survivors (54). Also, because of a paucity of studies focused specifically on reducing the symptoms of women who undergo premature menopause due to breast cancer treatments, best practices are largely extrapolated from management approaches for healthy postmenopausal women (or for survivors of postmenopausal breast cancer).

Managing hot flashes—Standard non-hormonal strategies to reduce hot flashes include lifestyle adjustments, mind-body techniques, and prescription medications.

Lifestyle adjustments: Weight loss is likely protective against hot flashes. The Women's Healthy Living and Eating study found that that weight gain was associated with worse hot flashes in mixed age breast cancer survivors, and there was a trend toward fewer hot flashes in those who lost at least 10 percent of their body weight (55). Although there are no data proving that it is helpful to dress in layers, keep the room temperature cool, and avoid alcohol, tobacco, and caffeine, these are all additional low-risk lifestyle adjustments that breast cancer survivors may consider (56).

Mind-Body Techniques: The mind-body connection may play a role in hot flash control such that relaxation may reduce a woman's hot flash burden. There are mixed data regarding the efficacy of paced respirations for management of hot flashes (57–61), but cognitive behavioral therapy (62, 63) and hypnosis (64, 65) do appear to reduce hot flash severity. In a randomized controlled trial (RCT) of 187 women who had at least 7 hot flashes per day, weekly hypnosis reduced hot flash scores by 80%, and cut physiologically monitored hot flashes by 57%, compared to an attention control technique ($p < 0.001$) (66). More recently, an RCT with a 2×2 randomization to venlafaxine, hypnosis, both, or neither found that hot flashes decreased by about 25% in the double control arm and by about 50% in each of the other 3 arms (suggesting that hypnosis may be as effective as venlafaxine, and that the two are not synergistic) (67). Acupuncture is also promising for this indication. Last year, Mao et al. reported on an RCT comparing acupuncture, sham acupuncture, gabapentin, and oral placebo. After two weeks of twice weekly acupuncture (real or sham) sessions followed by six weeks of weekly sessions, or three times a day gabapentin (or placebo) for eight weeks, the hot flash composite score fell most with acupuncture (−7.4) followed by sham acupuncture (−5.9), gabapentin (−5.2), and placebo (−3.4), with $p < 0.001$ (68). However, despite these data supporting the efficacy of hypnosis and acupuncture for treating hot flashes, access to these treatments is limited and most insurers do not cover these services.

Medications: A variety of non-prescription supplements have failed to demonstrate that they reduce hot flashes in placebo-controlled double-blinded RCTs. These include soy products (69–71), black cohosh (72), magnesium oxide (73), flaxseed (74) and vitamin E

(75). Prescription drugs that do seem to reduce hot flashes include clonidine (76, 77) selective serotonergic and/or noradrenergic reuptake inhibitors (SSRIs and/or SNRIs) (78–88), and gabapentin (89–92). Clonidine is less useful because of its substantial side effects (e.g., constipation, dizziness, drowsiness, and hypotension), and gabapentinoids also commonly cause lightheadedness and drowsiness, so SSRIs and SNRIs are often first-line treatments for hot flashes. In an unblinded cross-over trial that randomized breast cancer survivors to receive gabapentin versus venlafaxine, twice as many participants preferred venlafaxine (93). Paroxetine, an SSRI, is the only FDA-approved treatment for hot flashes, but it is less appealing in survivors who are taking tamoxifen because it inhibits cytochrome p450 2D6, and therefore theoretically could impair the efficacy of tamoxifen. Venlafaxine and citalopram are excellent options for breast cancer survivors who are experiencing bothersome hot flashes due to premature menopause.

Managing vaginal dryness—Because aromatase inhibitors (AIs) generally cause more vaginal dryness than tamoxifen (94, 95), switching from an AI to tamoxifen should be considered in breast cancer survivors who are suffering bothersome vaginal dryness during AI treatment.

In addition, treatment of vaginal dryness after premature menopause in breast cancer survivors should include the avoidance of irritants (e.g., soaps, detergents, and other products with perfumes or dyes) and the use of lubricants (water, silicone, or oil-based) before and during sexual activity. Vaginal moisturizers should also be applied 2–5 times per week. Hyaluronic acid (HLA) gel, a biopolymer that moisturizes vaginal tissue when applied every three days, improved vaginal symptoms as much as estriol cream did in one RCT in the general population of postmenopausal women (96). Another non-hormonal approach that might improve vaginal health is a CO₂ laser (97, 98), though long-term safety data are not available, and cost may be prohibitive. In addition, topical lidocaine applied to the vaginal introitus may improve insertional dyspareunia (99). If sexual activity is painful, vaginal dilators with or without pelvic floor physical therapy can be considered. Regular, painless sexual activity may promote vaginal health, as may the use of a vibrator to increase blood flow (100). Individual and/or couples counseling can help women improve sexual functioning.

If these non-hormonal approaches fail, and symptoms are severe, low-dose vaginal hormonal preparations are sometimes considered. Vaginal estrogens (e.g., 25 µg estradiol vaginal tablets and the low-dose vaginal ring) do increase circulating estradiol levels in women on aromatase inhibitors, so this approach is generally reserved for women taking tamoxifen (101, 102). Even 10 µg estradiol vaginal tablets likely have some systemic effect in patients receiving aromatase inhibitors (103). Vaginal testosterone or DHEA may be a better option for patients who are taking AIs, as neither increases circulating estrogens in this setting (104).

CARDIAC TOXICITY

Who is affected?—Breast cancer treatments can cause acute or chronic cardiac toxicities including congestive heart failure (CHF). Trastuzumab can be cardiotoxic (105), but most

episodes of trastuzumab-induced cardiomyopathy resolve with drug cessation. In contrast, anthracycline-based chemotherapy carries a dose-dependent risk of irreversible cardiac damage, and the clinical evidence of CHF often does not appear for years after the final anthracycline dose was administered (106, 107). In an Italian study of early stage breast cancer survivors, the rate of cardiac systolic dysfunction at 11 years median follow-up was 8% after doxorubicin-based chemotherapy and only 2% after non-anthracycline-based chemotherapy (108). However, the median cumulative dose of doxorubicin in those patients was 294mg/m² (higher than patients typically receive today), and the exact increased risk of symptomatic CHF remains uncertain with modern doses of anthracyclines. In BCIRG 001, an RCT comparing six cycles of FAC (5-fluorouracil-doxorubicin-cyclophosphamide) to six cycles of TAC (docetaxel-doxorubicin-cyclophosphamide), the incidence of mild to severe CHF was only 0.1% at 5 years median follow-up (109), but clinical trial participants are usually healthier than the general population. It is clear that certain populations are at greater risk of cardiac toxicity, including the elderly as well as patients with hypertension and/or diabetes (110).

What can be done?—When a non-anthracycline-containing regimen (such as docetaxel-cyclophosphamide) is available, thoughtful regimen selection can minimize risk of cardiotoxicity. This is particularly valuable in patients who are at increased risk of cardiac compromise due to age and/or comorbidities. Any patient with evidence of cardiac compromise that develops during or after anthracycline or trastuzumab treatment should be referred to a cardiologist for assessment and management. Dexrazoxane has been shown to reduce the incidence of anthracycline-induced cardiomyopathy, but due to cost and toxicity, it is only recommended in patients with advanced disease who have received at least 300mg/m² of doxorubicin or 540mg/m² of epirubicin and who plan to continue receiving an anthracycline. Beta blockers and ace inhibitors are relatively inexpensive and well-tolerated drugs that have also been of interest to prevent and treat cardiotoxicity from anthracyclines and trastuzumab (111–113). The PRADA study, a recent RCT of candesartan and/or metoprolol during anthracycline-based chemotherapy for early stage breast cancer, found no cardioprotection from metoprolol but less decline in EF with candesartan (0.8% vs. 2.6% with placebo). Additional research is needed to assess whether or not angiotensin receptor blockers like candesartan are the most effective drugs for treatment of chemotherapy-induced cardiomyopathy, and what role beta blockers and statins should play in this setting.

COGNITIVE DYSFUNCTION

Self-perceived cognitive dysfunction is very common in breast cancer survivors and can significantly impact quality of life in this patient population (114). During or after breast cancer treatment, many patients report memory and attention deficits in addition to word-finding difficulties and general impairments in cognitive functioning (115). Results from the 2010 LIVESTRONG study (which included a wide range of cancer survivors) showed that approximately half of the study participants (45.7%) reported self-perceived cognitive dysfunction, with no greater incidence in breast cancer survivors compared with in survivors of other tumors (116).

Over the past two decades, neuropsychological studies have attributed cognitive deficits to the neurotoxic effects of chemotherapy (117) because several cross-sectional studies demonstrated lower scores than expected on neuropsychological testing after chemotherapy (118). With the emergence of prospective data, it has been noted that cognitive deficits may be present in a substantial number of patients before adjuvant or neoadjuvant chemotherapy begins (119), implying that the etiology of cognitive dysfunction in this setting may be multifactorial (120). Additionally, endocrine therapy has also been linked to cognitive decline in this setting (121). Large scale prospective studies noted a subtle cognitive decline in a select subset of cognitive domains in 15–25 % of patients (122), although significantly higher rates were reported in some series (123). Further, results of a meta-analysis of several neuropsychological studies noted only small residual cognitive deficits in verbal and visuospatial ability at least 6 months after the completion of standard chemotherapy (124). Clearly, there is an element of dissonance between objective neuropsychological parameters and subjective complaints reported by patients (125). This may be because the testing instruments fail to record certain impediments and the fact that even subtle cognitive deficits may seriously impact highly functioning individuals. Additionally, the presence of severe deficits in some women may be masked by the presence of predominantly normal or near normal test results when data from different groups are amalgamated.

More recent studies have focused on the use of neuroimaging techniques (in particular, MRI) to identify correlates of cognitive deficits and complaints, and several structural and functional central nervous system (CNS) deficits have been found (126, 127). The findings to date suggest that there are neurological correlates to the cognitive complaints of breast cancer patients, but the majority of these studies are cross-sectional and exploratory in nature. Therefore, the degree to which chemotherapy influences cognitive functioning in cancer patients remains unclear; other treatments such as radiotherapy and endocrine therapy, along with fatigue, insomnia, co-existing depression, and the psychological stress of a cancer diagnosis, may also contribute.

Patients seek interventions to improve their cognitive symptoms (128). Results from a mixed-method systematic review of modifiable factors and cognitive dysfunction in breast cancer survivors showed that lifestyle factors such as stress management, physical activity, and sleep quality may be targets for behavioral intervention in this setting (129). Other potential strategies include mindfulness-based stress reduction (MBSR) techniques (130). Additionally, the use of cognitive therapy protocols to improve attention, memory and processing speed after chemotherapy is promising. For example, a small randomized trial of 47 breast cancer survivors who reported chemotherapy-related cognitive dysfunction showed that effective Memory and Attention Adaptation Training (MAAT) could be delivered through videoconferencing (131). This is an important observation as this treatment option could also help facilitate access to other survivorship services. Further, acetylcholinesterase inhibitors such as donepezil may moderately improve cognitive impairment in this setting (131). In a randomized, placebo-controlled study of donepezil in 62 female breast cancer survivors with self-reported cognitive dysfunction one to five years following chemotherapy, the donepezil group performed significantly better than the control group on two parameters of memory-the Hopkins Verbal Learning Test-Revised (HVLT-R) Total Recall ($p = 0.033$)

and HVLTR Discrimination ($p = 0.036$). No significant differences on other cognitive variables, subjective cognitive function, or quality of life were noted.

Conclusion

The survivorship care of breast cancer patients is extremely important. Breast cancer survivors experience a multitude of treatment sequelae, for which it is imperative that oncologists are skilled in providing counseling and treatment.

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