Early and Late Long-Term Effects of Adjuvant Chemotherapy

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OVERVIEW

Adjuvant chemotherapy continues to play an important role in breast cancer management. Exposure to chemotherapy can lead to a variety of early and late long-term toxicities, including ovarian failure (with resultant infertility and sexual dysfunction), bone loss, weight gain, neurotoxicity, neurocognitive changes, cardiac toxicity and secondary malignancy. Although chemotherapy effects may vary in medical severity, all effects have the potential to lead to a decrease in quality of life and a decrement on overall health status. Improved understanding of the etiology and management of chemotherapy-related toxicity may allow optimization of patient selection for treatment and ameliorate the concerns of patients who are considering embarking on a chemotherapy program. This article presents an overview of relevant early and late long-term toxicities, with a focus on recent advances and clinical management.

With the advent of genomic testing, rates of use of adjuvant chemotherapy for breast cancer have been in decline,1 although chemotherapy continues to play a significant role in the adjuvant therapy of patients with triple-negative and HER2-positive disease. Administration of chemotherapy can reduce risk of breast cancer recurrence and is generally considered tolerable with the use of contemporary supportive care, however, exposure to typical regimens may lead to both early and late toxicities. Given the estimated 3 million breast cancer survivors in the United States, many women are at risk of chemotherapy-related effects. Improved understanding of the etiology and management of chemotherapy-related toxicity may allow optimization of patient selection for chemotherapy and ameliorate the concerns of patients who are considering embarking on a chemotherapy program.

OVARIAN FAILURE: PREMATURE MENOPAUSE, INFERTILITY, SEXUAL DYSFUNCTION

Chemotherapy-induced premature ovarian failure is a noteworthy toxicity for premenopausal women receiving adjuvant chemotherapy. Although the majority of women may experience temporary amenorrhea, in many, ovarian function will return in the months following completion of treatment. However, a subset will experience permanent chemotherapy-induced ovarian failure, with the risk of permanent menopause increasing with age and modulated by chemotherapy type and duration.2,3 An implied additional cost of infertility exists for patients who sustain permanent amenorrhea. For patients with hormone receptor–positive cancers, infertility can also occur secondary to natural ovarian aging during long-term endocrine therapy. Even for patients who regain menses after chemotherapy, there may be an increased likelihood of premature menopause (under age 45) in patients who receive chemotherapy at a younger age.4 Concerns over risks of infertility can be substantial for young patients with breast cancer and may influence treatment selection.5,6 Pretherapy referral to a fertility specialist for a discussion of fertility preservation may help alleviate concerns and is endorsed by ASCO guidelines.7,8 Assisted reproductive technologies may be considered for patients facing infertility after treatment, although there are theoretical concerns about ovarian stimulation in the setting of hormone receptor–positive cancer. Specialty consultation to discuss newer techniques, including ovarian stimulation with aromatase inhibitors, is recommended.9 Available data to date do not suggest adverse outcomes in patients who become pregnant after a breast cancer diagnosis, regardless of hormone receptor status of the tumor.9

One of the most prominent early effects of ovarian failure can be frequent and disruptive hot flashes, which may be accentuated by concomitant use of adjuvant endocrine therapy. Multiple management techniques have been evaluated10,11; commonly used strategies include behavior modification, antidepressants, clonidine, gabapentin, vitamin E, and acupuncture.12-14 Data to date do not conclusively suggest inferior outcomes after concurrent use of CYP2D6-inhibiting antidepressants and tamoxifen; however, recent prescribing trends have supported a shift toward greater use of weak CYP2D6-inhibiting antidepressants in breast cancer survivors.15 Atrophic vaginitis is another common and significant side effect which can lead to dysuria, frequent urinary tract infections, pruritus, and dyspareunia. Nonhormone lubricants (both

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Author’s disclosures of potential conflicts of interest are found at the end of this article.

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water-based and silicone) are typically recommended, particularly in a patient with a history of hormone receptor–positive breast cancer. Topical vaginal estrogen therapy may be a more effective approach, although estrogen levels have been noted to rise with local estrogen delivery, no signal of increased risk of cancer recurrence has been noted. Additional recommended lifestyle interventions include increased sexual activity and Kegel exercises to improve pelvic muscle tone.

Sexual dysfunction is a common sequelae of treatment-related ovarian failure, and can be manifest by decreased libido, dyspareunia, and difficulty with orgasm; it is estimated to affect up to 50% of all breast cancer survivors, particularly those who experience treatment-related ovarian failure. The etiology of sexual dysfunction is multifactorial, likely reflecting not only reduced levels of estrogen, but also the psychologic trauma of cancer diagnosis and treatment for a young woman. Specific interventions may include vaginal lubricants, avoidance of concomitant medications which decrease libido, and counseling with a sexual health specialist.

**WEIGHT GAIN**

It has long been recognized that women who receive adjuvant chemotherapy for breast cancer gain weight, on average about 10 lb. Reasons for weight gain are likely multifactorial, including changes in activity level, menopausal status, endocrine manipulation, diet, metabolism, and mood. Results of observational studies describing the effect of weight gain after a breast cancer diagnosis on future disease recurrence have been variable, although analyses from the Nurses’ Health Study and other studies have suggested weight gain may increase risk of disease recurrence. Diet and exercise interventions have demonstrated success in preventing weight gain or stimulating weight loss, and current guidelines for exercise training in early cancer survivors have been published. All efforts should be made to encourage breast cancer survivors to “avoid inactivity” and pursue a more active lifestyle.

**BONE LOSS**

Loss of bone density is a common occurrence in both pre- and postmenopausal breast cancer survivors. Proposed etiologies include premature menopause as well as the effect of breast cancer therapies, specifically aromatase inhibitors, on circulating estrogen levels. The development of decreased bone density may have significant health consequences. In an analysis from the Women’s Health Initiative, increased fracture risk was seen in postmenopausal breast cancer survivors compared with participants without breast cancer. A variety of guidelines for bone health screening and management of osteopenia and osteoporosis have been published. In general, it is recommended to screen at-risk individuals for osteoporosis by dual-energy x-ray absorptiometry every 1 to 2 years, and consider initiation of bisphosphonate therapy for scores defining osteoporosis. Other maneuvers, including pursuing weight-bearing exercise and adequate calcium and vitamin D, are generally recommended for breast cancer survivors.

**NEUROPATHY**

Peripheral sensory or motor neuropathy can occur after exposure to microtubule inhibitors such as taxanes. Sensory neuropathy can be characterized by both paresthesias and pain, which can significantly affect a patient’s quality of life. Rates and severity of taxane-related neuropathy vary and reflect agent selection, dose, schedule, and comorbidities. Supportive management during treatment typically includes dose modification and treatment delay; supplemental preventative agents including glutathione, acetyl-L-carnitine, and alpha-lipoic acid are under investigation. Although some patients will experience gradual improvement in neuropathy, many are left with residual and potentially disabling symptoms. Multiple management techniques have been evaluated, including use of gabapentin or venlafaxine, for which there is supportive data from a randomized trial. CALGB 170601, a randomized phase III trial of duloxetine for painful chemotherapy-induced neuropathy, demonstrated reductions in pain scores with duloxetine compared with placebo. Investigation of additional nonpharmacologic modalities is ongoing.

Ultimately, best management of peripheral neuropathy would be avoidance of the toxicity through identification of individuals at greatest risk. One path of investigation has suggested higher paclitaxel acute pain syndrome (P-APS) scores with first dose of chemotherapy may correlate with peripheral neuropathy. Pharmacogenomic analysis has identified single nucleotide polymorphisms (SNPs) associated with the development of moderate to severe peripheral neuropathy after paclitaxel exposure. Reassuringly, the development of neuropathy does not appear to be correlated with chemotherapy efficacy, therefore supporting the safety of further development of predictive biomarkers for neurotoxicity, including SNPs or P-APS scores, which may allow modification of adjuvant chemotherapy selection to reduce the risk of permanent disabling neuropathy.

**KEY POINTS**

- Adjuvant chemotherapy can lead to early and late long-term side effects for breast cancer survivors.
- Given the number of breast cancer survivors, many women are at risk of experiencing toxicity.
- Effects of chemotherapy vary in severity, but can often negatively affect quality of life and overall health status.
- Management of long-term chemotherapy-related toxicity involves screening for symptoms, use of supportive medication, and referral for specialty consultation as needed.
- Ongoing research is evaluating both the etiology of toxicity as well as effective interventions.
CARDIAC DYSFUNCTION

The most common chemotherapy-related cardiotoxicity observed in breast cancer survivors is left ventricular dysfunction. Although cyclophosphamide and taxanes have been associated with a variety of cardiac complications, the most common agents implicated in adjuvant therapy after chemotherapy are anthracyclines and trastuzumab.

Anthracycline-mediated cardiotoxicity can occur in an acute or subacute fashion, however, the majority of cases are late-onset, occurring at least 1 year after completion of therapy. Late-onset cardiotoxicity tends to be irreversible, is related to cumulative anthracycline dose, and may reflect a variety of intracellular mechanisms including free radical formation. Although absolute rates of anthracycline-related cardiac dysfunction in clinical trials generally have been low, analysis of nontrial older populations through the Surveillance, Epidemiology, and End Results (SEER) database suggests the incidence may be higher, with a rate of CHF of 38.4% in patients with breast cancer ages 66 to 70 treated with adjuvant anthracycline-based therapy compared with 29% in those who did not get chemotherapy.

Exposure to trastuzumab, the highly effective monoclonal antibody for HER2-positive breast cancer, may lead to cardiac dysfunction following a different pattern than anthracycline-mediated toxicity: typically occurring during time of medication administration, and generally reversible with a hold in therapy and use of cardiac medication. It has been proposed that the differential patterns of cardiotoxicity between the two agents reflect divergent mechanisms of action, with anthracyclines causing permanent cardiomyocyte apoptosis and necrosis, and trastuzumab leading to temporary cellular changes. Rates of asymptomatic or severe cardiac dysfunction in the major trials of adjuvant trastuzumab have varied from a maximum of 4.1% with a standard anthracycline-containing regimen, to 0.6% to 1.87% in regimens without concurrent chemotherapy and trastuzumab or without anthracyclines. Rates of asymptomatic drop in cardiac function are higher, in the range of 17% to 19% after anthracycline exposure in the major adjuvant trials. Reassuringly, long-term follow-up from the adjuvant trastuzumab trials have suggested late cardiotoxicity events related to trastuzumab appear to be rare. Routine evaluation of cardiac function is recommended for patients receiving ongoing trastuzumab; however, following completion of therapy, further cardiac evaluation is symptom-driven only.

Prechemotherapy identification of individuals at risk of cardiac toxicity would improve selection of chemotherapy regimens. Clinical risk factors predictive of cardiotoxicity have included older age, pre-existing hypertension, low baseline left ventricular ejection fraction, and elevated body mass index. Long-term follow-up data from NSABP B-31 have been used to construct a Cardiac Risk Score, incorporating age and left ventricular ejection fraction (LVEF), to predict risk of a cardiac event. Novel imaging, including echocardiographic techniques with greater sensitivity to discern subclinical cardiac dysfunction, and potentially concurrent use of cardiac biomarkers, may have even more promise as predictive tools. There is no clear role for routine screening for left ventricular dysfunction in breast cancer survivors in the absence of clinical symptoms, however, for survivors with suspected cardiac toxicity, imaging with echocardiography and referral to cardiology are strongly recommended.

NEUROCOGNITIVE DYSFUNCTION

Neurocognitive changes after chemotherapy exposure, termed “chemo-brain,” are a source of serious concern and anxiety for breast cancer survivors. It is estimated up to 75% of women who receive chemotherapy will report a change in cognitive function in the 2 years after treatment. Patients typically describe problems with attention, memory, and concentration.

Studies to date have been complicated by small sample size, diverse definitions of cognitive impairment, and variable pre-exposure assessments of cognitive function. Additionally, studies evaluating cognitive dysfunction during chemotherapy present divergent results from those using a postchemotherapy time-point. Early cross-sectional studies demonstrated increased cognitive impairment in patients with breast cancer during and after chemotherapy when compared with healthy matched controls. Subsequently, prospective longitudinal studies have suggested evidence of postchemotherapy change in cognitive dysfunction, at least in a subset of patients. A recent meta-analysis has analyzed 17 studies evaluating cognitive functioning in the post-chemotherapy period, confirming small deficits in verbal ability and visuospatial control in patients at least 6 months

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<th>Table 1. Summary of Complications with Adjuvant Chemotherapy</th>
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<td><strong>Toxicity</strong></td>
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out from chemotherapy compared with testing prechemotherapy or in healthy participants. Studies evaluating pre- and post chemotherapy imaging have also attempted to investigate anatomic correlates of cognitive deficits; small prospective trials using MRI have suggested both structural changes and changes in brain activation after chemotherapy exposure.

It has been proposed, however, that the etiology of cognitive dysfunction is likely multifactorial; although exposure to chemotherapy may contribute, other factors are likely relevant as well, including other modalities of treatment (surgery, radiotherapy, endocrine therapy), supportive care medications, menopausal symptoms, anxiety, depression, fatigue, or other comorbid conditions. An International Cognition and Cancer Task Force has suggested a subgroup of patients may be especially sensitive to neurocognitive effects of chemotherapy, including those of advanced age or lower cognitive reserve. Furthermore, genetic polymorphisms in susceptibility genes, including apolipoprotein E (APOE) and catechol-O-methyltransferase (COMT) may identify individuals with vulnerability to cognitive dysfunction after chemotherapy. Variability in age and polymorphism distribution may explain the variability in results in some of the prospective cognitive studies to date. There is interest in whether prophylactic or therapeutic interventions, including the psychostimulant modafinil, fluoxetine, or structured cognitive behavioral therapy, may improve symptoms. Further work is necessary to confirm if individuals at particularly high risk of cognitive change can be identified in advance to protect from exposures or treat with preventative medication, while providing reassurance to others who may be unlikely to experience this toxicity.

SECONDARY MALIGNANCY

One of the rarest yet most feared long-term toxicities of adjuvant chemotherapy is hematologic malignancy, specifically myelodysplasia (MDS) or acute myeloid leukemia (AML). The etiology of this complication is thought to reflect exposure to topoisomerase II–targeted agents (anthracyclines) or alkylating agents (cyclophosphamide), which are frequently included in adjuvant chemotherapy regimens. Topoisomerase II–related myeloid malignancies may present within 5 years of exposure, may not be preceded by MDS, and may have abnormal cytogenetics of 11q23. Alkylator-related malignancies present after a longer duration of time, may be preceded by MDS, and may have cytogenetic abnormalities of chromosomes 5 and 7. The risk of secondary malignancy appears to reflect increased cumulative dose exposure, although most series report population rates of less than 1%. Concurrent use of growth factors to support “dose-dense” scheduling, or radiotherapy, may contribute a slight additional risk of myeloid malignancy, although these topics remain under investigation.

Older patients are thought to be at increased risk of myeloid complications, although they have typically been excluded from analysis of younger cohorts who participate in clinical trials. A SEER-Medicare population-based analysis of over 64,000 older patients with breast cancer (median age 76) suggested a small but significant increase in the risk of developing AML after chemotherapy, with a hazard ratio of 1.53 (p = 0.005), although absolute risks at 10 years remain small (1.8% with chemotherapy vs. 1.2% without chemotherapy). Analysis of over 21,000 patients in the National Comprehensive Cancer Network (NCCN) suggested a 10-year rate of MDS/AML of 0.27%, with a slight additional increase in those who had received adjuvant chemotherapy.

Methods to reduce exposure to potentially bone marrow-toxic chemotherapy may help reduce the risk of secondary myeloid malignancies. Adjuvant regimens which replace anthracycline with a taxane have demonstrated slightly decreased rates of secondary myeloid malignancies, and could be considered in a situation where risk of myeloid malignancy is a significant concern. Specific predictors of future MDS/AML are not known, however, continued use of genomic tools to better identify chemotherapy-sensitive tumors would help improve the risk/benefit ratio for this toxicity by reducing chemotherapy exposure in patients unlikely to receive anticancer benefit.

CONCLUSION

Despite the gains in reduction of cancer recurrence with administration of adjuvant chemotherapy, breast cancer survivors may be exposed to risks of both short- and long-term toxicities after chemotherapy. Although chemotherapy effects may vary in medical severity, all effects have the potential to lead to a decrease in quality of life and a decrement on overall health status. Improved management of the effects of chemotherapy will require better understanding of management strategies, and larger prospective trials evaluating a variety of interventions are underway. Additionally, for the first time, the 2013 NCCN Guidelines will include guidelines for screening breast cancer survivors for many of the common short- and long-term effects from therapy (Ligibel L., personal communication, 2013). After decades of recognition of many of the detrimental effects of treatment, it is hoped that future clinical and research activities will definitively reduce adverse therapy-related outcomes for breast cancer survivors.
References


