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Chemotherapy-Induced Ovarian Failure

Manifestations and Management

Julian R. Molina, Debra L. Barton and *Charles L. Loprinzi*

Department of Oncology, Mayo Clinic, Rochester, Minnesota, USA

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Abstract

Thanks to improvements in treatment regimens, more and more patients are now surviving cancer. However, cancer survivors are faced with the serious long-term effects of the different modalities of cancer treatments. One of these adverse effects is chemotherapy-induced irreversible damage to the ovarian tissues, which leads to premature ovarian failure and its resulting consequences such as hot flashes, osteoporosis, sexual dysfunction and the risk of infertility. Chemotherapy-induced ovarian failure (or chemotherapy-induced premature menopause) affects the quality of life of female cancer survivors. Although there is no clear definition of chemotherapy-induced ovarian failure, irreversible amenorrhoea lasting for several months (>12 months) following chemotherapy and a follicle stimulating hormone level of ≥30 MIU/mL in the presence of a negative pregnancy test seems to be an appropriate characterisation. Different chemotherapy agents, alkylating cytotoxics in particular, have the potential to cause progressive and irreversible damage to the ovaries. The result of this damage is a state of premature ovarian failure, with progressive declining of estrogen levels, decreasing bone mass and an increased risk of fractures. Historically, hormonal replacement therapy (HRT) has been used to treat menopausal problems in the general population, but concerns about the potential of estrogen to increase the risk of breast cancer in women at high-risk or increase the risk of recurrence in cancer survivors, have forced physicians to utilise alternative treatments. This review discusses some of the newer therapies that are now available to provide appropri-

ate symptom control, avoid complications such as fractures and possibly prevent infertility by making the ovarian epithelium less susceptible to cytotoxic agents.

Recent advances in cancer treatment have resulted in significant long-term survival improvements for cancer patients.[1-4] It is estimated that 62% of adult cancer patients and 77% of paediatric cancer patients survive beyond the 5-year mark.[5] The population of long-term cancer survivors continues to grow on an annual basis and is expected to continue to grow in the future. These long-term survivors are faced with iatrogenic effects from the different cancer treatment modalities. In particular, chemotherapy-induced ovarian failure has a significant effect on the quality of life of female cancer survivors. This is a particular concern because of the young age of many of the patients who survive cancer.[6-11]

In ovarian failure or menopause the ovary is depleted of follicles and is thus unable to produce estradiol and other female hormones. The resulting decreased levels of estradiol increase the production of follicle stimulating hormone (FSH) by the pituitary gland. In a healthy menstruating woman, FSH will stimulate follicular granulosa cells in the ovaries to produce estradiol. Since no feedback inhibition is present after ovarian damage, the end result is an increase in FSH and luteinising hormone levels, and decreased circulating levels of estrogen and progesterone.[12] This endocrine profile, which is normally seen in women undergoing a natural menopause, is also observed with chemotherapy-induced ovarian failure. Histologically, a marked loss of primordial follicles is seen in ovarian biopsies after chemotherapy-induced ovarian failure, as is also seen in normal menopause.[13]

Although there is no clear definition of chemotherapy-induced ovarian failure, irreversible amenorrhoea lasting for several months (>12 months) following chemotherapy and a FSH level of ≥30 MIU/mL in the presence of a negative pregnancy test seems to be an appropriate characterisation.

Different chemotherapeutic agents have been shown to affect ovarian function to varying degrees, with alkylating agents being among the most damaging.[14,15] The ability of adjuvant chemotherapy alone to induce amenorrhoea is variable and depends on both the regimen and the age of the patient. The average percentage of chemotherapy-related amenorrhoea after a combination regimen of cyclophosphamide, methotrexate and fluorouracil, administered for at least 3 months, is 76% (range 49–100%) for women aged ≥40 years, but only 40% (range 21–71%) in women aged <40 years.[11]

The extent of ovarian dysfunction from chemotherapy is determined by a patient's age, prior or concurrent use of radiation therapy and the total dose of chemotherapy administered, with older women at an increased risk of chemotherapy-induced ovarian failure even when they are subjected to comparatively low doses of chemotherapy.[15]

The chaotic hormonal state of a natural menopause is even more pronounced after chemotherapy-induced menopause. The rapid changes in hormone levels associated with chemotherapy can lead to more severe symptoms than those associated with the more gradual decline in estrogen levels during normal aging.[16,17] Women who are closer to the age of natural menopause often experience more severe symptoms when treated for breast cancer, which suggests that the natural, age-related symptoms are exacerbated by adjuvant therapy or tamoxifen, a commonly prescribed hormonal medication for breast cancer.[17]

Historically, hormonal replacement therapy (HRT) has frequently been used to treat menopausal problems in the general population, but concerns about the potential of estrogen to increase the risk of breast cancer in women at high-risk or increase the risk of recurrence in cancer survivors, have forced physicians to utilise alternative treatments. Although long-term HRT has a beneficial effect on women's bones, this beneficial effect is often offset by an increased risk of venous thromboembolic disease, breast cancer, stroke, cognitive dysfunction and coronary artery disease.[18] Data from a trial by Li et al.,[19] demonstrated that the use of combined HRT is associated with an increased risk of breast cancer, particularly invasive lobular tumours. Moreover, the use of combined hormone therapy has been shown to decrease both the sensitivity and the specificity of mammography because of the increase in

radiographic breast density, which makes the diagnosis of breast cancer more difficult.[20] In addition, data from recent studies show that the routine use of HRT in women does not increase quality of life.[21,22] Taking these results together, the use of HRT to treat women with chemotherapy-induced ovarian failure should be carefully discussed with the patient on an individual basis; it cannot be widely recommended.[23]

In this review we will discuss issues related to the effects associated with hormone deprivation due to chemotherapy-induced ovarian failure, including the management of resultant problems.

1. Osteoporosis

Osteoporosis is a state of decreased bone mass associated with changes in the microarchitecture of the bone that results in an increased risk of fracture and may cause substantial morbidity and mortality.[24,25] Osteoporosis is defined by the WHO as a bone mineral density (BMD) of ≥2.5 standard deviations below the mean for age- and sex-matched young adults (designated as a T-score of <2.5).[26] Osteopenia, a state of less severe thinning of the bones, is defined as a T-score between −1 and −2.5.[26]

Menopause is clearly associated with osteoporosis. In addition to menopause, other risk factors associated with osteoporosis in the general population include older age, Northern European ethnicity, Caucasian race, low bodyweight, positive family history of osteoporosis, dietary calcium deficiency, lack of weight-bearing physical activity, certain medications, cigarette smoking, heavy alcohol use, trauma and some chronic diseases, such as thyroid problems, adrenal disease, liver dysfunction, rheumatic disease and malabsorption.[24,27] Women who have received chemotherapy are at increased risk for osteoporosis for several reasons: chemotherapy-induced ovarian failure with resulting premature menopause, a direct effect of the adjuvant treatment on BMD, poor intake of calcium and vitamin D and a direct effect of the cancer itself.[28-35] Certain kinds of cancer, such as breast cancer, can cause a direct increase in osteoclastic activity, which may result in an increased risk of osteoporosis.[32,33] Attesting to this notion is a study of 88 women with recurrent breast cancer and 352 women with recently diagnosed breast cancer that found a 6-fold ($p < 0.0001$) increased risk of vertebral fracture for the group of women with recurrent breast cancer compared with the group of newly diagnosed cases or to a group of normal controls. Women who had bone metastasis at the time of enrolment or those who developed them during the follow-up were excluded from the final analysis, which suggested that this effect was independent of the presence of bone metastasis.[28,29]

The accelerated bone loss seen in women that experienced menopause after chemotherapy has been clearly demonstrated in several studies. In a study of 49 premenopausal women who were treated with adjuvant chemotherapy for breast cancer, a median decrease in BMD of 6.3% in the lumbar spine, 3.9% in the femoral neck and 3.8% in the greater trochanter was detected.[30] For the group that developed chemotherapy-induced ovarian failure, median decreases in BMD of 7.7% in the lumbar spine and 4.6% in the femoral neck were observed.[30] Other investigators have reported similar findings after chemotherapy for breast cancer.[31-33]

During normal menopause, declining serum estrogen levels are associated with an increase in osteoclast-mediated bone reabsorption and subsequent bone loss.[34] Although osteoblast activity also increases, the amount of bone that is reabsorbed is greater than that formed at each remodelling site. The end result is an accelerated bone loss that is responsible for a 20–30% loss of cancellous bone and a 5–10% loss of cortical bone. This rapid bone loss occurs within a few years after menopause and is thought to represent 50% of lifetime spinal bone loss in women.[34]

Besides estrogen, testosterone also plays an important role in the regulation of BMD. In postmenopausal women, the conversion of adrenal androgens to estrogen by the enzyme, aromatase, leads to continued low levels of circulating estrogen in postmenopausal women; these hormones are also important for regulation of calcium homeostasis through their effects on renal and gastrointestinal absorption of calcium.[34] Estrogen deficiency, in particular, is responsible for a decrease in intestinal calcium reabsorption and an increase in renal fractional calcium excretion. These changes lead to an increase in parathyroid hormone, which explains the

persistent increase in bone turnover after the accelerated initial loss due to estrogen deficiency.[34-37]

It is estimated that 22% of women with breast cancer are premenopausal at the time of diagnosis.[28] From this group, 63–96% of patients will develop chemotherapy-induced ovarian failure within 1 year of receiving cyclophosphamide-containing adjuvant chemotherapy treatment.[28] Chemotherapy agents commonly used for the treatment of female cancers, such as methotrexate and doxorubicin, have been shown, in animal models, to affect BMD.[38-40] Premenopausal women with non-metastatic breast cancer have higher than average rates of bone loss and a risk of vertebral fractures nearly five times that of the general population.[29] Bone loss is greatest in women who become amenorrheic as a result of chemotherapy, which suggests that estrogen deficiency is an important aetiological factor.[30,31] In a study of 27 breast cancer survivors, the BMD of women who became amenorrheic after chemotherapy was 14% lower than that of menstruating women.[28] Two other studies evaluated lumbar spine BMD in women at baseline and after chemotherapy for localised breast cancer. At 2 years, bone loss ranged from 4.4% in one study to 5.9% in the other; bone loss was as high as 9.5% in women who became amenorrheic during chemotherapy.[30,31] Another study compared 44 women with breast cancer treated with adjuvant chemotherapy to 44 women who did not require adjuvant chemotherapy. The chemotherapy treated group had a decreased BMD of 1.29 g/cm^2 compared with a decrease of 1.12 g/cm^2 in the untreated group. This study again suggested that bone loss was greatest in women who became amenorrheic as a result of chemotherapy.[32]

Other additional factors also increase the risk of osteoporosis in women with cancer. Estrogen-blocking therapies (i.e. tamoxifen) or ovarian ablation therapy in premenopausal women who are treated for breast cancer, aromatase inhibition, physical inactivity, use of corticosteroids and inadequate intake of calcium and vitamin D can all contribute to the increased osteoporosis risk seen in cancer survivors.[28,30,31,38-42] The loss of total body bone can be ≥5% in premenopausal women with breast cancer that is treated with ovarian ablation.[43] These osteoporosis-facilitating effects are not only seen as a consequence of chemotherapy. Tamoxifen, a commonly prescribed adjuvant hormonal treatment for breast cancer, has mixed agonist and antagonist effects on estrogen receptors and has different effects on BMD that depend on the menopausal status of the patient at the time of treatment.[42-48] Repeat BMDs were determined in a study of 179 pre- and postmenopausal women who received either adjuvant tamoxifen or placebo. The premenopausal group treated with tamoxifen experienced a 1.4% greater decrease in BMD per year over the 3-year study than the placebo-treated premenopausal group.[42] In contrast, postmenopausal women who were treated with tamoxifen experienced a comparable increase in BMD compared with postmenopausal women treated with placebo.[42] Similar protective effects of tamoxifen in postmenopausal women have been reported by other investigators.[44-46] It is believed that a partial agonist activity of tamoxifen confers a net benefit in postmenopausal women, with minimal circulating estrogen, although this partial agonist effect is not as strong as natural estrogen in premenopausal women.[46] This agonist effect in women with high circulating estrogen levels (premonopausal) actually blunts the estrogenic activity on bones that is normally seen with premenopausal females.[47-50] In premonopausal women with breast cancer, treatment with tamoxifen also reduces the markers of bone turnover.[51]

Raloxifene, another selective estrogen receptor modulator now widely used as adjuvant hormonal therapy for breast cancer, also reduces the risk of fractures from osteoporosis in postmenopausal women.[52] The effects of this agent in premenopausal women are currently unknown. There is, however, some preliminary data that suggests there is cross-resistance between tamoxifen and raloxifene on breast cancer cells and, thus, that raloxifene may not be an appropriate preventive agent for osteoporosis in women who have been previously treated with tamoxifen.[53] Raloxifene reduces bone turnover in postmenopausal women by 25%, with an increase in BMD of about 2% at the spine and hip. The risk of vertebral fracture is decreased by 30–50%, with no effect on the risk for non-vertebral fractures.[54]

Newer agents that are used to treat breast cancer, such as aromatase inhibitors, are designed to almost

completely eliminate endogenous estrogen production.[55,56] As might be predicted, this therapy has an effect on bone metabolism.[57,58] An analysis of BMD and bone turnover was done in a subgroup of 308 postmenopausal women who were treated as part of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.[59] In this study, the control arm comprised 46 breast cancer patients who did not receive hormonal therapy. Bone reabsorption was measured with urinary N-telopeptide and free deoxypyridinoline, and bone formation was assessed by measuring bone alkaline phosphatase levels. At 1 year, therapy with anastrozole was associated with bone loss in the spine and hip, most notably at the spine where the BMD was reduced from baseline by 2.6%, compared with a 0.4% reduction in healthy controls. Tamoxifen therapy, on the other hand, increased the BMD and decreased the markers of bone turnover. The ATAC researchers concluded that treatment with anastrozole increased bone remodelling and bone loss and increased subsequent fracture risk.[59]

Estrogen administration, which is known to reduce bone turnover and the rate of bone loss, with a resulting increase in BMD in postmenopausal women, has classically been considered to be contraindicated in patients with hormone-responsive cancers.[60,61] Moreover, as soon as estrogen therapy is discontinued, BMD begins to decline at a rate that is similar to that observed before initiation of estrogen therapy.[62]

Other approaches to the prevention and treatment of chemotherapy-induced osteoporosis include the use of calcium, vitamin D and bisphosphonates. Calcium and vitamin D supplementation are associated with a 20–25% reduction in the risk of fractures among elderly women.[63] Calcium is also of critical importance, not only for the treatment of established osteoporosis, but also for the prevention of osteoporosis in patients at risk. Women at risk for chemotherapy-induced ovarian failure with normal BMD or meeting criteria for osteopenia on dual energy x-ray absorptiometry (DEXA), should receive prophylactic treatment to prevent osteoporosis. Prophylaxis includes calcium (1000–1500mg of elemental calcium daily) and vitamin D (400–800IU daily), which have been shown to reduce hip and vertebral fracture by 43% and 32%, respectively.[63-65] Other measures, such as smoking cessation and maintaining weight-bearing physical activity, should also be recommended to groups at high risk.

Bisphosphonates are pyrophosphate analogues that are avidly adsorbed to bone surfaces.[66,67] They reduce bone turnover by specifically inhibiting osteoclastic bone reabsorption. The precise mechanism by which bisphosphonates inhibit osteoclast function is not fully understood, but may include a direct toxic effect on mature osteoclasts, an inhibition of osteoclast production from precursor cells and/or an impairment of osteoclast chemotaxis to sites of active bone.[68-72] Alendronic acid and risedronic acid, the most extensively studied bisphosphonates, reduce vertebral and hip fractures by 50% in women with osteoporosis and prevent bone loss in perimenopausal and postmenopausal women with no osteoporosis at baseline.[73-76] Clinical trials suggest that these drugs prevent bone loss as effectively as the recommended dose of estrogen in standard HRT regimens.[77] In addition, unlike estrogen, bisphosphonates can be discontinued without causing rapidly accelerated bone loss.[78] Newer, more potent bisphosphonates now in the market include zoledronic acid and ibandronic acid. The pre-clinical safety (toxicology) profile of zoledronic acid is in general similar to that of other bisphosphonates, but this compound appears to produce fewer and/or less severe adverse events at what are considered to be pharmacologically effective doses.[79,80] What is even more promising is the fact that the intravenous second and third generation bisphosphonates can be given every 3 months, and possibly every 6–12 months, to achieve maximal effects on bone loss.[81]

Bisphosphonates can also restore bone in patients with osteolytic lesions that are associated with breast cancer or multiple myeloma. Studies in patients receiving zoledronic acid at doses ranging from 2mg to 4mg every month have shown an 11% increase in lumbar spine BMD, with the 4 mg/month dosage being more effective.[82] Clodronic acid, an oral bisphosphonate, was evaluated in two randomised, placebo-controlled trials of early stage breast cancer patients.[31,83] In one of these studies, oral clodronic acid, taken for 2 years, was efficacious in preventing bone loss after chemotherapy. By 1 year, the BMD had fallen by 2.2% in the

placebo group and had risen by 0.2% in the clodronic acid group (mean difference of 2.4%).[31] In the second trial done in premenopausal women receiving chemotherapy with cyclophosphamide, methotrexate and fluorouracil, the clodronic acid and placebo groups differed in lumbar spine BMD by 3% at 1 year and by 3.7% at 2 years ($p < 0.01$). More interesting, an analysis of the subgroup of patients who developed ovarian failure showed a 5.9% bone loss in the lumbar spine for the clodronic acid group versus 9.5% in the placebo group ($p < 0.001$). In both groups, the treatment was well tolerated, with no differences in adverse events between the two study arms.[30] Two of the bisphosphonates described previously, alendronic acid and risedronic acid, are now US FDA approved for both the treatment and prevention of osteoporosis in women in general. Nonetheless, the use of bisphosphonates (e.g. alendronic acid, clodronic acid, zoledronic acid and risedronic acid) for primary prevention of osteoporosis in cancer patients is currently undergoing more thorough evaluation in cancer survivors and their use is not yet established as standard clinical practice.[30,31,84,85]

Calcitonin, also a FDA-approved treatment for osteoporosis, appears to be less efficacious than the bisphosphonates, with respect to improvement of BMD and actual reduction of fracture rates.[86]

2. Sexual Dysfunction

Problems with sexual dysfunction are very prevalent among women treated with chemotherapy, with estimates that they occur in up to 60% of breast cancer survivors.[87] A study of quality of life in long-term breast cancer survivors by Ganz et al.[88] found a decrease in sexual activity from 65% activity at baseline to 55% at follow-up 5 or 10 years later. Sexual dysfunction is increased in women who have been treated with adjuvant chemotherapy.[89,90] A study by Young-McCaughan[91] compared sexual dysfunction between women treated for cancer with chemotherapy and women treated with endocrine-based therapy. Women treated with chemotherapy were three times more likely to report decreased libido, seven times more likely to have trouble reaching orgasm and six times more likely to describe vaginal dryness and pain with intercourse. In a recent study, Ganz et al.[92] investigated the baseline psychosocial status of women enrolled in a randomised trial that tested two psychosocial interventions for women at the end of primary treatment. Sexual functioning was worse for women who received chemotherapy than for those who did not, regardless of the type of surgery ($p < 0.001$). Some of these effects appear to be the direct result of chemotherapy, but they may also be due to the effects of surgery or radiation therapy.[87,93,94] Many women are hesitant to discuss sexual dysfunction with their healthcare providers; however, when questioned, 96% of them report at least one problem, including problems with desire (libido), lubrication, anorgasmy, dyspareunia and satisfaction.[87,93,94] Sexual dysfunction tends to worsen over the first several years of primary breast cancer adjuvant chemotherapy treatment, but improves with longer follow-up.[95,96] In fact, 10-year breast cancer survivors report similar levels of sexual functioning regardless of whether they have received prior chemotherapy.[96]

Hormone-based therapy with tamoxifen does not appear to cause sexual dysfunction, despite tamoxifen being associated with symptoms such as vaginal discharge.[88,91,97,98] A study of 1098 breast cancer survivors 1–5 years after primary breast cancer treatment found that women who had been treated with tamoxifen ($n = 305$) did not report an increase in sexual dysfunction.[98] Comparing women on tamoxifen to a group of non-cancer controls, Mortimer et al.[97] likewise found no differences in sexual desire, sexual arousal or the ability to achieve orgasm. The lack of effect of tamoxifen on sexual dysfunction can not be extrapolated to other endocrine-based therapies. In particular, treatment of breast cancer using the gonadotropin-releasing hormone (GnRH) agonist goserelin in combination with tamoxifen was associated with increased sexual dysfunction when compared with the group of patients treated with goserelin alone; the reason for this is not clear. Interestingly, in this same study, tamoxifen as a single agent did not produce sexual dysfunction.[99]

Changes in female sexual behaviour among cancer survivors may not only be due to chemotherapy effects on the ovary; they may also be the result of the type of surgical intervention performed or the use of radiation therapy. This point may be particu-

larly important for gynecological and breast cancer survivors who are especially susceptible to sexual dysfunction because of the change in body image that results after surgery.[89,100] However, while breast-conserving surgical procedures have shown benefits over mastectomy with regard to body image, most studies find no difference between lumpectomy versus mastectomy in regards to sexual functioning.[89,93,100-104] For example, in a study by Ganz et al.[92] of breast conservation versus mastectomy, no difference in sexual dysfunction or quality of life was seen between the two groups 1 year after the procedure. Likewise, studies done 4–8 years after breast cancer surgery found no differences in sexual function between patients treated with mastectomy or breast conservation surgery.[89,102] The effect of mastectomy or breast conservation surgery on feelings of sexuality may depend on patient age; if age is counted as a significant factor in a patient's self image, lumpectomy may have a more beneficial effect on quality of life for younger women. However, the relationship of self-image to sexual function is not entirely clear.[102]

2.1 Treatment of Sexual Dysfunction

2.1.1 Non-Pharmacological Interventions

Treatment of sexual dysfunction requires comprehensive assessment and intervention. Counselling to evaluate and enhance the patient's perception of body image and self as an attractive sexual being can play an important role in the treatment of sexual dysfunction. Counselling should go beyond the standard techniques and include behavioural techniques aimed at decreasing anxiety, fear and self-doubts related to sexual activity.[105] A controlled trial by Ganz et al.[106] that used a comprehensive menopausal assessment intervention program (CMA), evaluated the various outcomes of postmenopausal women with breast cancer. This study provided patients with a psychological intervention and with treatment options for hot flashes, vaginal dryness and urinary symptoms. Symptoms of sexual dysfunction improved significantly, including frequency and interest in sex for self and partner.[105] Greendale et al.[105] studied 61 postmenopausal breast cancer survivors who were participants in a randomised, controlled trial of non-hormonal interventions for menopause symptoms and who had a partnered, intimate relationship. The outcomes were standardised scales of sexual interest, dysfunction and satisfaction. In this small sample of breast cancer survivors, the authors found multiple correlates of sexuality that were modifiable by psychological intervention.

2.1.2 Pharmacological Interventions

Vaginal Lubricants

Data from several studies also suggest that vaginal dryness may play a significant, if not central, role in sexual dysfunction after chemotherapy.[90,93,106-108] Vaginal lubricants and moisturisers can be used to treat symptoms of dryness or for lubrication and may indirectly improve other sexual problems as well.[93,105,107-109] A prospective study in cancer survivors reported that women using polycarbophil had decreased vaginal dryness equal to that of women using a water-soluble lubricating placebo; however, the decrease in dyspareunia was significantly better with polycarbophil than with the placebo lubricant.[108]

Topical Vaginal Estrogen

Topical estrogen preparations appear to alleviate vaginal dryness more effectively than non-estrogenic vaginal preparations do. At least three formulations exist that are associated with minimal systemic absorption: Estring® [1] is an estrogen-impregnated ring that is inserted into the vagina, where it releases small amounts of estrogen over a 12-week period;[110] Vagifem® is a vaginal estrogen tablet that is also inserted into the vagina with an applicator; and a small dose of Premarin® vaginal cream can be helpful to some patients.[111]

Testosterone Supplementation

Multiple retrospective and prospective randomised, placebo-controlled studies support the use of testosterone to improve libido, sexual motivation and, in general, sexual dysfunction among menopausal women.[111] However, there are concerns about the potential toxic and cancer-promoting effect of testosterone treatment for cancer survivors.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

In particular, the potential for testosterone to increase estrogen levels, and thereby theoretically increase the risk of breast cancer recurrence, should be acknowledged prior to its use outside a clinical trial.[112] Studies of testosterone supplementation in breast cancer survivors are currently in development.[108,113]

3. Vasomotor Instability

Vasomotor instability usually presents as hot flashes, but can also be seen as night sweats and night time awakenings. It begins 1–2 years prior to menopause and persists for 6 months–5 years or longer after menopause. Hot flashes are characterised by the sudden onset of a sensation of intense warmth that typically begins in the chest and progresses to the neck and face. They are often accompanied by anxiety, palpitations, profuse sweating and red blotching of the skin. Hot flash symptoms can affect a women's ability to work, her social life, her sleep pattern and her general perception of health.[114-118] When they occur in cancer patients, these symptoms can also affect patient quality of life, as well as compliance with therapy and satisfaction with treatment decisions. The cause of vasomotor symptoms in breast cancer patients could be the result of abrupt estrogen loss due to surgery or chemotherapy, from tamoxifen or other hormonal therapies and from discontinuation of HRT or natural menopause. Hot flashes affect about three-fourths of all postmenopausal women and are the most commonly described health problem among this age group.[119]

The physiology of hot flashes is still unclear. It has been postulated that changes in circulating estrogen levels can induce abnormalities of the central thermoregulatory centres, which results in hot flashes.[120] Perspiration and vasodilatation, classic mechanisms of heat loss controlled by the hypothalamus, are activated during a hot flash.[120] In normal homeostasis, the thermoregulatory centre maintains the core body temperature in a tightly regulated range called the 'thermoregulatory zone'. Complex neuroendocrine pathways that may involve noradrenaline (norepinephrine), serotonin, estrogen, testosterone and endorphins appear to govern the regulation of this thermoregulatory nucleus and are possible sites where dysfunction may occur.[120-122] Recent studies show that in up to 60% of hot flash episodes a trigger that precipitates small changes in core body temperatures occurs prior to hot flashes. These studies suggest that subtle increases in temperature prior to a hot flash, coupled with a narrow homeostatic temperature zone, may release the heat loss mechanisms that lead to hot flash symptoms. Investigators have identified predictors of subsequent hot flash problems. Some of these triggers include drinking hot coffee, cold drinks or just minor changes in the room temperature.[123] Hot flashes in women undergoing natural menopause are associated with a maternal history of hot flashes as well as with cigarette smoking;[123] whereas a prior history of moderate to severe hot flashes with menopause and a history of prior estrogen therapy use are predictive for subsequent tamoxifen-associated hot flash problems in breast cancer survivors.[122]

Hot flashes are the most common reason women seek estrogen replacement therapy and, although estrogen effectively relieves symptoms for 80–90% of women who initiate treatment,[124-126] women with a history of breast, ovarian or uterine cancer, venous thromboembolism or a family history of breast cancer comprise large populations for whom estrogen therapy may be contraindicated.[127-138] Increasing evidence also suggests that women with a recent myocardial infarction or established coronary artery disease may be poor candidates for estrogen therapy.[139,140] Finally, results from the Women's Health Initiative (WHI) trial, in combination with other reports, suggested that long-term combined estrogen and progesterone therapy may not be as beneficial for women as was once believed.[22,136-138,140-143] For this reason, many women have assumed that hot flashes are an inevitable symptom of being a breast cancer survivor.

Tamoxifen is associated with hot flashes in >50% of users.[144-147] Tamoxifen-associated hot flashes increase in postmenopausal women over the first several months of treatment and then gradually resolve.[145]

It is difficult to evaluate the efficacy of pharmacological therapy for hot flashes with anecdotal reports alone because of placebo effects. Multiple placebo-controlled trials demonstrate a 20–35% reduction in hot flashes with 4 weeks of placebo treatment.[148-153] These studies suggest that one in

five women will have at least a 50% reduction in hot flashes with a placebo alone and one in ten such women will have at least a 75% reduction. For individuals with mild symptoms that do not interfere with sleep or daily function, treatment with vitamin E (800IU once daily) represents a reasonable initial approach. A randomised, crossover, placebo-controlled trial in 120 women found that, in addition to the placebo effect, vitamin E therapy decreased the average hot flash frequency by one episode per day.[150] The low cost and minimal adverse effects of vitamin E make a trial of this agent reasonable despite its modest benefits. The effect of vitamin E may not be apparent for several weeks; therefore requiring an adequate trial to assess its efficacy.

Several clinical trials have investigated soy protein, a prominent source of phytoestrogen, for the treatment of hot flashes. The results are mixed, but suggest that soy protein (90–400 mg/day) and isolated isoflavones do not reduce hot flashes.[151,154-160] Furthermore, the long-term safety of pharmacological doses of soy in patients with a history of breast or uterine cancer is not established. To explore the systemic hormonal effects of soy, several trials evaluated endometrial thickness, vaginal cytology and uterine artery pulsatile index.[156,157,160] No differences between soy- and placebo-treated patients are reported. Although reassuring, these surrogate endpoints and the short follow-up period cannot establish the safety of pharmacological soy use in women with a history of breast cancer.

The newer antidepressant agents represent promising non-hormonal options for the treatment of hot flashes. Venlafaxine, a serotonin re-uptake inhibitor (at lower doses) and a profound inhibitor of noradrenaline re-uptake (at higher doses) is an effective agent for controlling hot flashes. In a double-blind, placebo-controlled trial of 191 women randomised to placebo or to one of three venlafaxine doses (37.5mg, 75mg or 150mg daily), the placebo group had a 27% reduction in hot flashes after 4 weeks of treatment versus 40%, 61% and 61% reductions, respectively, in the three venlafaxine groups.[153] The adverse effects observed with venlafaxine included dry mouth, decreased appetite, nausea and constipation (the latter only at dosages of 150 mg/day).[153]

Selective serotonin re-uptake inhibitors (SSRIs) are also effective for the treatment of hot flashes. An open-label, pilot study of paroxetine suggested a degree of efficacy similar to that seen with venlafaxine.[152,153,161] Subsequent randomised, double-blind, placebo-controlled trials confirmed that paroxetine decreased hot flashes significantly more than did placebo (to a similar degree to what had been previously reported with venlafaxine) and that it was relatively well tolerated.[162,163] A randomised, double-blind, crossover, placebo-controlled clinical trial demonstrated that fluoxetine reduces the incidence of hot flashes, although the reduction does not appear to be as great as that observed with either venlafaxine or paroxetine.[152] No significant toxicity was observed in this trial.

Gabapentin, a gamma-aminobutyric acid (GABA) analogue that has most commonly been used to treat a variety of neurological disorders, was recently reported by anecdotal experience to be a promising new therapy for the relief of hot flashes.[164,165] A double-blind, placebo-controlled trial of gabapentin for hot flashes recently confirmed these findings and demonstrated that this drug reduces hot flashes significantly more than placebo does.[163] The adverse effects include lightheadedness and sleepiness early on, which generally resolve with continued treatment. Some women also develop a rash and oedema, the latter of which appears to be related to decreased serum albumin levels.[163]

Veralipride, a benzamide derivative with antidopaminergic effects, is also effective against menopausal symptoms; however, veralipride in not currently available in the US and can cause dystonic reactions.[166-168] Clonidine, methyldopa and belladonna alkaloids do not appear to be as effective as gabapentin or the newer antidepressants for hot flashes control and can be associated with significant adverse effects.[148]

Despite anecdotal reports, the benefits of herbal therapies in clinical trials have been disappointing to date. Herbal treatments, such as black cohosh (*Cimicifuga racemosa*) and a standardised blend of twelve Chinese herbs,[169,170] have been prospectively evaluated and have shown only minimal activity. Another placebo-controlled trial of black cohosh is currently ongoing to more definitively determine whether this agent might be helpful. Some recent

reports have called to attention the possible toxic effects of black cohosh in the liver. A report from Australia recently described six patients with acute hepatitis, associated with the long-term intake of various herbal medicines, including two patients who were taking black cohosh.[171] However, a cause and effect relationship between black cohosh and hepatotoxicity is still unproven.

Progestational agents such as megestrol and medroxyprogesterone represent a reasonable alternative for the treatment of hot flashes in patients not responsive to non-hormonal medication. A double-blind, crossover placebo-controlled trial among breast and prostate cancer survivors found a 75–80% reduction in hot flashes with megestrol compared with a 20–25% reduction in the placebo group.[149] Lower doses (20mg) appear to be as effective as the 40mg dose, with an improved adverse effect profile.[172] Although minimal adverse effects were described during the treatment period, 31% of the women experienced withdrawal bleeding 1–4 weeks after the discontinuation of megestrol.[172] A 3-year follow-up analysis suggested that the benefits of megesterol might be long lasting.[173] An alternative progestational agent approach is to use intermittent intramuscular medroxyprogesterone.[174,175] However, it should be noted that there are no long-term prospective data to establish the safety of these progestational agents for women with some forms of cancer such as hormone-sensitive breast cancer.

4. Infertility

Treatment with chemotherapy can severely deplete the ovary of follicular stores, even in young patients,[176,177] which results in menstrual irregularities, ovarian failure and associated infertility.[6-8] The risk of infertility seems to be higher for males. A study done at Stanford University involving children survivors of Hodgkin's disease, showed azoospermia in 83% of the males and ovarian failure in only 13% of the females.[178] Infertility is also one of the main long-term adverse effects seen in survivors of haematology malignancies and breast cancer.[6,8,176,177] Histological studies have shown that the end result of some types of chemotherapy on human ovarian tissue is ovarian atrophy with a marked loss of primordial follicles.[13] Contrary to other tissues, such as the gastrointestinal tract and bone marrow where the effects of chemotherapy are reversible, in the ovaries there is a direct correlation between dose intensity and irreversibility of damage.[6,177]

Although for women with chemotherapy-induced infertility the suggested treatments are not always effective, several alternatives have been attempted to try to maintain fertility in younger females undergoing chemotherapy.

4.1 Prevention of Female Germ Line Damage from Chemotherapy

4.1.1 Gonadotropin-Releasing Hormone Analogue Treatment

Results of experiments in rats and primates have shown that GnRH analogues may protect the ovaries from the toxic effects of chemotherapy.[179] In initial murine studies done by Glode et al.,[180] treatment with a GnRH agonist resulted in gonadal protection from cyclophosphamide. It is possible that the decreased gonadal function induced by the secretion of pituitary gonadotropin prevents the follicles from reaching the chemotherapy-sensitive stage. This effect would be due to inhibition of the process of recruitment from the pool of small follicles into the pool of larger follicles that undergo further development and atresia.[181] For example, experiments in rhesus monkeys done by Ataya et al.[182] showed how a GnRH agonist protected against the cytotoxic effect of chemotherapy on the ovaries by inducing follicular depletion. Several studies have demonstrated a protective effect of GnRH agonist therapy on chemotherapy-induced ovarian follicular depletion in rats. However, a rat's estrous cycle duration is 4 days versus a 28-day menstrual cycle in women. Moreover, rats have estrous cycles without endometrial shedding, whereas women menstruate by shedding the endometrial lining. Finally, rat ovaries have been shown to contain GnRH receptors, whereas their existence in human ovaries is equivocal.[182] Nevertheless, the protective effect of monthly GnRH analogue injections versus placebo initiated before chemotherapy was documented in rhesus monkeys that, similar to humans, also appear to lack ovarian GnRH receptors.[182] Nonetheless, the protective effect of GnRH analogues may prove to be

insufficient against the usually prolonged, high-dose chemotherapy regimens given to cancer patients in contrast to the 1-month course used in most animal models. However, in a study by Blumenfeld et al.[183] a group of 18 premenopausal patients receiving chemotherapy for lymphoma were treated with a GnRH analogue prior to and during chemotherapy. This group was compared with a similar group of 16 lymphoma patients who were also treated with chemotherapy, but without the GnRH analogue. In the group treated with the GnRH analogue, 93.7% of the patients regained ovarian function compared with 39% in the group without GnRH analogue. In another study, the protective effect of a GnRH analogue on ovarian function was studied as a regimen added to the chemotherapy for breast cancer. After a follow-up of close to 5 years, 86% of the group on GnRHs was having normal menses.[183] Therefore, more studies aimed at determining the role of GnRH analogues for protection against chemotherapy-induced ovarian failure are urgently needed. Currently, female cancer patients have few options for fertility preservation. Although frozen embryo storage has been a standard procedure in *in vitro* fertilisation (IVF) centres since 1983; it is far from satisfactory for the preservation of reproductive potential in cancer survivors.

4.1.2 Future Alternatives

Improvement in oocyte cryopreservation may offer additional possibilities in the future. Among these cryopreservation alternatives are the cryopreservation of metaphase II oocytes, cryopreservation of fertilised ova or embryos and the transplantation of ovarian tissue.

The cryopreservation of metaphase II oocytes has been attempted with good results in mice, but the research in humans is still far from reality because of concerns about mutagenesis.[6] The cryopreservation of fertilised ova or embryos by means of IVF of retrieved oocytes could enable embryo freezing in some patients. However, this approach is seldom used because of many factors, including the lack of a current male partner, the need to postpone cancer therapy for a few weeks and the possibility that estrogen rise may be undesirable in cancer patients.[6,184] Finally, cryopreservation of ovarian cortex, which hosts thousands of immature follicles, has been proven to work in animals.[185-187] Concerns about the potential risk of transplanting tumours cells from the graft have limited research in humans. A more practical use of this approach would be to graft ovarian tissue that is capable of producing enough estrogen to prevent osteoporosis and vasomotor symptoms. Moreover, the prolonged culture of primordial and primary follicles *in vitro* is still unfeasible; transplantation of ovarian cortex theoretically might be used to obtain follicular maturation. However, more research is required to improve vascular supply to the graft and maintain prolonged activity of the transplanted ovarian tissue.

5. Conclusion

Significant improvements in survival from cancer have uncovered long-term adverse effects of chemotherapy. Among them, chemotherapy-induced ovarian failure is a common one that affects quality of life in female cancer survivors. The toxic effect of chemotherapy in the ovaries leads to osteoporosis, vasomotor symptoms such as hot flashes, sexual dysfunction and infertility. Although some advances have been made, more research is needed.

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Correspondence and offprints: Dr *Charles L. Loprinzi*, Department of Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
E-mail: loprinzi.charles@mayo.edu