# Life After Treatment: Quality-of-Life Concerns in Patients Treated for Cancer

Presented by Mindy E. Goldman, MD

## Abstract

Traditionally, the physical, psychological, and psychosocial long-term needs of cancer survivors have received little attention compared with screening for cancer recurrence and secondary cancers. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Survivorship offer recommendations for various survivorship concerns, and those for improving menopausal symptoms were presented at the NCCN 22nd Annual Conference. Key considerations in managing menopausal symptoms in cancer survivors were reviewed, with chemotherapy-induced amenorrhea, fertility concerns, and both hormonal and nonhormonal therapeutic options featured.

*J Natl Compr Canc Netw 2017;15(5.5):744–747*

"Menopause is often a frequently neglected area," declared Mindy E. Goldman, MD, Clinical Professor, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California San Francisco (UCSF), and a member of the Breast Oncology Program, UCSF Helen Diller Family Comprehensive Cancer Center. Yet menopausal complaints are common and often more severe in cancer survivors than in the general population. Dr. Goldman is a member of the NCCN Survivorship Panel, serving as subcommittee Chair on menopause-related symptoms and subcommittee Co-Chair on sexual function.

Although the clinical definition of menopause is 1 year without menses, it often does not apply to cancer survivors who have had prior chemotherapy or hormonal therapies to treat breast cancer. "In those situations, you may need to rely on menopausal levels of estradiol and follicle-stimulating hormone [FSH]," Dr. Goldman suggested. In addition, she added, recent data also suggest that antimüllerian hormone may be a relevant hormonal marker of ovarian reserve.[1]

Presented by Mindy E. Goldman, MD, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California San Francisco, and Breast Oncology Program, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California.

Dr. Goldman has disclosed that she has served as a scientific advisor for Madorra.

Correspondence: Mindy E. Goldman, MD, UCSF Helen Diller Family Comprehensive Cancer Center, 2356 Sutter Street, San Francisco, CA 94115. E-mail: mindy.goldman@ucsf.edu

Dr. Goldman briefly reviewed some of the common symptoms of menopause. "By far, hot flashes are the most common menopausal complaint, occurring in approximately 80% of women," she noted. Moreover, sleep problems may exist beyond the effect of hot flashes. "It has been shown that women don't get into a deep REM [rapid eye movement] sleep often after menopause," she said.

Dr. Goldman offered several possible reasons why menopausal symptoms are often more severe in cancer survivors: surgical treatments may include oophorectomy with immediate onset of surgical menopause; premenopausal women with normal menstrual functioning may have ovarian shutdown with chemotherapy; postmenopausal women taking hormone replacement therapy tend to abruptly stop when diagnosed with endocrine-dependent cancers; and vasomotor symptoms are common with hormonal drugs such as tamoxifen or aromatase inhibitors.

For Dr. Goldman, the key is to be sure that menopausal complaints are included in the assessment of cancer survivors. "You won't know if your patients are having these problems if you don't remember to ask," she stressed.

## Chemotherapy-Induced Amenorrhea

The incidence of ovarian failure depends on the chemotherapy regimen, cumulative dose, and patient age. Most ovarian toxicity is due to alkylating agents, with moderate effects from doxorubicin or cisplatin and fewer

effects from fluorouracil, methotrexate, vincristine, paclitaxel, and docetaxel.

This ovarian function in cancer survivors may be temporary or permanent. "When counseling patients, I generally tell them that if they are over age 40, there is less of a chance of menstrual function returning; if they are younger than age 40, there is a good chance their periods will return," Dr. Goldman said.

The question of whether chemotherapy-induced amenorrhea (CIA) has a prognostic impact on premenopausal breast cancer was addressed in a meta-analysis by Zhou et al.[2] They found that CIA contributed to an improved prognosis in premenopausal women with estrogen receptor–positive breast cancer. Dr. Goldman commented, "Not only are our treatments having direct cytotoxic effects but [they also have] indirect hormonal effects mediated by damage to ovarian estrogen-producing cells."

Many young women with newly diagnosed breast cancer have concerns about fertility and make decisions about cancer treatment based on fertility desires. In fact, a prospective study has shown that almost 30% of young women with breast cancer make treatment decisions based on fertility desires.[3]

The international randomized phase III POEMS trial studied whether chemotherapy with a gonadotropin-releasing hormone agonist such as goserelin would reduce the rate of ovarian failure in women with early hormone receptor–negative breast cancer.[4] The investigators reported that the addition of goserelin appeared to protect against ovarian failure. In fact, the researchers noted more pregnancies and live births, as well as better survival outcomes, in those who received goserelin.

## Treatment Options for Hot Flashes

Breast cancer survivors should be screened regularly for menopausal symptoms disruptive to quality of life, according to the NCCN Guidelines for Survivorship, with other causes ruled out (Figure 1). Tests include measurement of estradiol, FSH, luteinizing hormone, and prolactin levels as indicated. Treatment options for vasomotor symptoms include both nonhormonal and hormonal treatments (Figure 2), over-the-counter options, integrative therapies, and lifestyle interventions.

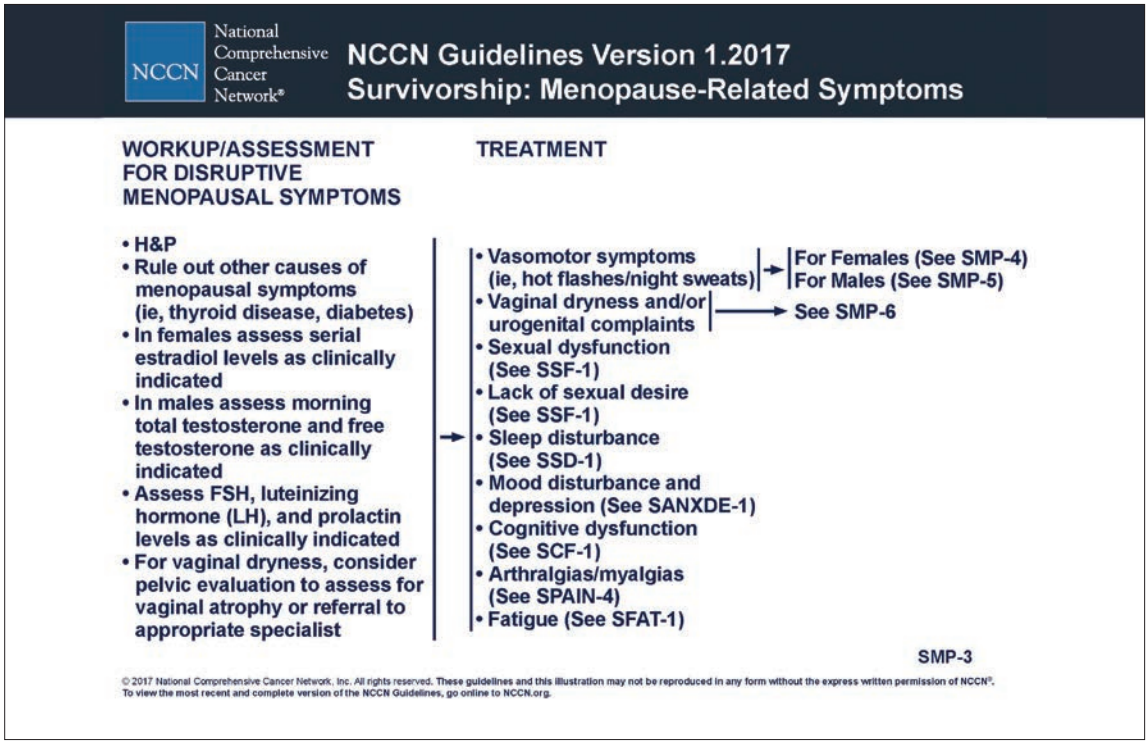


**Figure 1.** Workup for disruptive menopausal symptoms.

Over-the-counter treatment alternatives include phytoestrogens, botanicals, and dietary supplements (eg, vitamin E, black cohosh, soy). "Use of these options is incredibly common," admitted Dr. Goldman. However, although these agents have shown some benefits in noncancer populations, the data have been mixed on their effectiveness in cancer survivors.

Integrative therapies for hot flashes include acupuncture, exercise/physical activity, cognitive behavioral therapy, yoga, hypnosis, tai chi, and stellate ganglion blocks. Although some benefits have been reported with these therapies, Dr. Goldman warned they have limited evidence of safety and efficacy, and therefore have a category 2B ranking in the NCCN Guidelines.

Nonhormonal options include low-dose antidepressants, anticonvulsants, and neuropathic pain relievers. Although many antidepressants are included in the NCCN Guidelines, "the best data we have are for venlafaxine," said Dr. Goldman. Improvement of menopausal symptoms with venlafaxine can be achieved with doses much lower than for depression. "Although the benefits for depression could take weeks, the benefits for menopause are often seen within days," she noted. As a result of the lower doses, adverse effects are generally fewer. "Start with the lowest dose possible and increase as tolerated," suggested Dr. Goldman.

Another nonhormonal agent mentioned in the NCCN Guidelines is low-dose paroxetine. This 7.5-mg dosing is lower than that used for depression and is the only FDA-approved alternative to hormones for hot flashes. Because these pure selective serotonin reuptake inhibitors have the potential to interfere with the metabolism of tamoxifen, they should be used with caution for women taking tamoxifen.

Gabapentin is another nonhormonal option. Because it tends to cause sedation, it may be best given at night. Dr. Goldman noted that in women who have sleep difficulties, this side effect of gabapentin may actually be a plus.

As for hormonal therapy, "We know that hormones are the most effective therapy for treating vasomotor symptoms," declared Dr. Goldman. Again, clinicians should use the lowest dose possible to control symptoms. There are also many formulations of hormones available, thus treatment is often best managed by a gynecologist or other women's health provider.

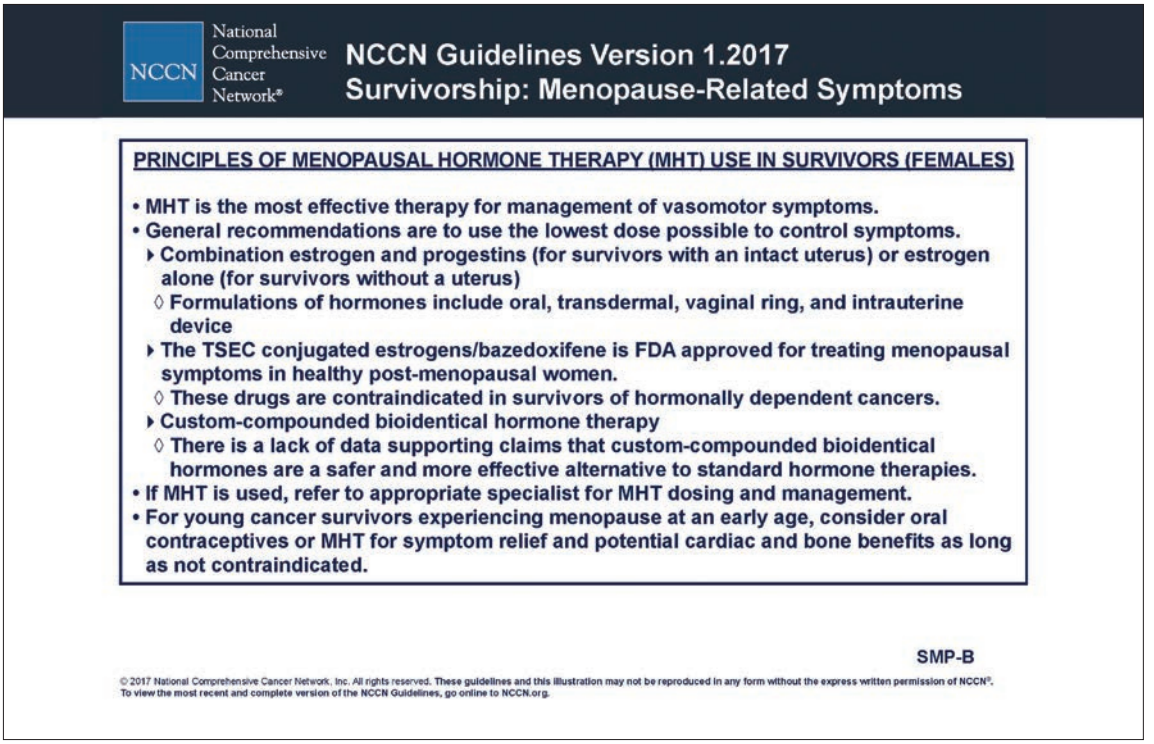


**Figure 2.** Principles of menopausal hormone therapy use in female cancer survivors.

## Managing Other Symptoms

Dr. Goldman briefly discussed vaginal dryness, urogenital complaints, and decreased libido. Similar to the management of menopausal symptoms, the NCCN Guidelines recommendations suggest nonhormonal options first, despite limited data on their efficacy. These options include lubricants, moisturizers, gels, and oils; local estrogen is also an alternative, although it has a category 2B designation. Research has shown that local estrogen is preferred over systemic estrogen for vaginal dryness. Additionally, these come in different formulations including estrogen creams, ring formulation, and suppositories.

One novel treatment of vaginal dryness highlighted by Dr. Goldman is a microablative carbon dioxide laser. Approved by the FDA in 2014 for skin resurfacing, it acts to improve collagen production in the vagina. Data from a 12-week prospective trial showed an improvement in vulvovaginal atrophy in postmenopausal women.[5] "I think the initial results are promising but very early, and I would like to see more data," she said. Also, this isn't something that is covered by insurance, and women pay an average of $3,000 out of pocket.

Among the urogenital complaints of menopausal women are urethral discomfort, urinary frequency, hematuria, dysuria, and increased frequency of urinary tract infections. Treatment options typically involve the use of local estrogens in addition to the targeted urinary symptoms.

Finally, Dr. Goldman briefly mentioned the NCCN Guidelines recommendations on sexual function, which were presented last year at the NCCN 21st Annual Conference. The connection between vaginal dryness and sexual function is key. "It is important to treat the vaginal dryness first and then address specific sexual complaints," she emphasized.

Lastly, pharmacologic options were discussed for improving painful sex, and include the selective estrogen receptor modulator ospemifene that is FDA-approved for use in menopausal women. However, this hasn't been studied in women with endocrine-sensitive cancers, thus is contraindicated. A new novel agent that has also gotten FDA approval is prasterone, a vaginal preparation of DHEA; this is expected to be on the US market in summer 2017, but is also currently contraindicated in women with a history of estrogen-dependent cancers. Overall, these newer options highlight the interest in developing new and novel ways of addressing vaginal dryness and female sexual functioning.

## References

1. Fréour T, Barrière P, Masson D. Anti-müllerian hormone levels and evolution in women of reproductive age with breast cancer treated with chemotherapy. Eur J Cancer 2017;74:1–8.
2. Zhou Q, Yin W, Du Y, et al. Prognostic impact of chemotherapy-induced amenorrhea on premenopausal breast cancer: a meta-analysis of the literature. Menopause 2015:22:1091–1097.
3. Ruddy KJ, Gelber SI, Tamimi RM, et al. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. J Clin Oncol 2014;32:1151–1156.
4. Moore HC, Unger JM, Phillips KA, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med 2015;372:923–932.
5. Perino A, Calligaro A, Forlani F, et al. Vulvo-vaginal atrophy: a new treatment modality using thermo-ablative fractional CO2 laser. Maturitas 2015;80:296–301.