Estrogen Deficiency: In Search of Symptom Control and Sexuality

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Menopausal symptoms can be very prominent problems in women as they approach the age of 50 years and beyond. For at least three reasons, such problems are exacerbated in patients who have had breast cancer. First, cytotoxic chemotherapy in premenopausal women can cause an abrupt menopause, with marked symptoms. Second, the most commonly used antineoplastic drug in the world, tamoxifen, causes, as its most prominent toxic effect, hot flashes. Third, estrogen therapy, the most widely used treatment of women with menopausal symptoms, is often not used in patients with a history of breast cancer because of concerns about what estrogen might do regarding breast cancer.

The article by Ganz et al. (1) in this issue of the Journal describes a group of breast cancer survivors with marked menopausal-associated symptoms. This study incorporated a number of design strengths. The authors used a randomized study method with a control group. Well-established instruments were chosen to measure symptoms and quality of life at baseline and at follow-up times. Sound statistical methods were employed, and the report was clearly written.

To summarize the study results, Ganz et al. report that the use of a nurse practitioner, in a tailored comprehensive menopausal assessment intervention program, led to a statistically significant decrease in menopausal symptoms and a statistically significant improvement in sexual function in women compared with a group of women without such intervention who served as a control group. These authors conclude that such a program is feasible, is acceptable to patients, and leads to both a decrease in menopausal symptoms and an increase in sexual functioning.

Agreeing with these conclusions, what are the limitations of this study? The authors rightly report that one of the limitations of their study is that it was not placebo controlled. Understanding that there is no easy manner to provide a placebo control, using the design of this study, how much does this lack of a placebo control influence the study results? A substantial influence is suggested by noting that placebos will decrease hot flashes over a 4-week period of time by approximately 20%–25% (2–5). Also noteworthy is that, in one trial, there was a tendency for an improvement in libido and a decrease in depressive symptoms in patients who were randomly assigned to receive a placebo (6). Thus, the placebo component of participating in a specialized clinic might have a substantial influence on the study outcomes.

A second limitation of the results from this study is that the effects of the various components of the treatments provided (education, counseling, and medications) cannot be discerned. A third limitation deals with the transferability of the intervention to practice at other sites and, hence, the ability to replicate the results. The outcomes from this trial, as indicated by the authors, came from one nurse practitioner who was intensively trained by a physician with substantial interest and expertise in the evaluation and treatment of menopausal symptoms in breast cancer survivors. This process is not necessarily transportable to other clinical situations. While being one of the limitations of the study, the fact that the intervention was delivered by one person is also a strength. One of the most difficult issues in implementing psychosocial/behavioral interventions is ensuring the consistency of the intervention across subjects. By having the intervention delivered by one person, some consistency is assured.

One of the key findings of this study relates to sexual functioning. The women in the study reported multiple issues related to sexual functioning. Problems with sexual functioning in the study women appeared to be associated with vaginal dryness and with psychosocial aspects of well-being and relationships. Although this article suggests that enhanced anatomic competence, that being vaginal lubrication, was primarily responsible for various positive outcomes, it would be remiss not to emphasize the possible critical role of the educational/counseling part of the intervention. The measurement tool used for the sexual functioning outcome included eight items, some of a physiologic, and others of a psychosocial, nature. The intervention group improved in all eight items, while the usual-care group improved in only two of the three physical items. The nature of these results presents evidence that the educational/counseling component of the intervention may have contributed a great deal to these outcomes. It is important to note that the assessment of sexual functioning can lead to interventions that can have positive outcomes and that this can be done by a trained nurse. Sexuality concerns are too often not addressed in this patient population, and this study provides a strong incentive to begin to bring these issues to light and to provide long overdue assistance to patients and their significant others.

In addition to addressing sexuality issues, the other primary goal of this work was the relief of target menopausal symptoms: hot flashes, vaginal dryness, and urinary incontinence. Let us take this opportunity to briefly discuss newer information regarding individual treatment modalities for the treatment of specific menopausal symptoms. Much of this information became elucidated after the clinic and protocol by Ganz et al. were designed.

The pharmacologic interventions used in this study for hot flashes were Bellergal, clonidine, and megestrol acetate. Clonidine has a similar degree of efficacy as vitamin E, or maybe a bit more (3,5,7). This benefit from clonidine, which is a bit better...

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than that ascribed to a placebo, comes with some significant toxic effects (mouth dryness, dizziness, drowsiness, and sleeping difficulties). This can limit its utility and patient acceptance, which may be responsible for why only 13 of the intervention patients (39%) used it.

Megestrol acetate or other progestational agents such as medroxyprogesterone acetate decrease hot flashes to a degree of magnitude similar to that seen with estrogen (2). This therapy is generally well tolerated but is limited by theoretical concern by patients and physicians regarding the use of any hormonal therapy in patients with a history of breast cancer.

A new class of agents, the newer antidepressants, has recently demonstrated efficacy for alleviating hot flashes (6,8,9). These agents appear to decrease hot flashes by 50%–60%, a benefit that is higher than that seen by any other class of nonhormonal agents. Although these antidepressants do have some associated toxic effects, they are relatively well tolerated by most patients. Further exploration is ongoing to compare and contrast many of the newer antidepressants in an attempt to find the most efficacious and least toxic therapy for this clinical problem.

Migrating from hot flashes to vaginal dryness/urinary incontinence, it is clear that the latter is less well studied. Nonetheless, vaginal moisturizers do appear to provide some mild-to-moderate clinical benefit for vaginal dryness (10). Given the limited utility of nonhormonal means of treating vaginal dryness, however, many practitioners feel comfortable using local estrogen therapy for treatment of these vaginal symptoms. This can be used with either a vaginal cream or an estrogen ring. Although some estrogen is systemically absorbed with this therapy, its risks, in terms of breast cancer, appear to be minimal, if any.

What about the use of systemic hormonal therapy (estrogen and/or progesterone) in breast cancer survivors? It has been standard clinical practice, as understood by most physicians, to not use estrogen therapy in patients who previously have had breast cancer. This long-held viewpoint has been relatively recently endorsed by scientific and clinical experts as discussed in the proceedings of a consensus conference (11). Understanding this, it is noteworthy that data from a series of pilot or phase II clinical trials suggest that providing estrogen therapy to selected populations of women with a past history of breast cancer is relatively safe (12,13). In fact, some of these trials, which have used epidemiologic methods for providing matched control populations, have suggested that the patients receiving estrogen replacement therapy have actually done better than their matched historic control subjects. Caution is always in order, however, when using data from clinical studies that are neither randomized nor placebo controlled. To this end, however, there is an ongoing randomized placebo-controlled clinical trial that has been discussed previously (14). This clinical trial, which randomly assigns selected breast cancer survivors to receive estrogen (with or without progesterone) or a placebo, now has 80 patients who were entered in a randomized study and followed for at least 4 years, 60 of whom have been followed for at least 5 years (Vassilopoulou-Sellin R: personal communication). The results of this clinical trial are awaited anxiously. Given the lack of proof of any substantial negative impact associated with systemic estrogen in breast cancer survivors, it appears reasonable to use systemic estrogen in selected women with past histories of breast cancer who understand the theoretical risks associated with using systemic estrogen.

In conclusion, menopausal symptoms in breast cancer survivors are a prominent problem that deserve the attention of cancer research, education, and practice groups. To this end, the article by Ganz et al. (1) is a welcome addition to the medical literature.

REFERENCES