Impact of Tamoxifen Adjuvant Therapy on Symptoms, Functioning, and Quality of Life

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This article reviews the symptoms and everyday problems associated with tamoxifen adjuvant therapy and their impact on patients' quality of life. In addition, the purported toxic effects of tamoxifen therapy (e.g., premature menopause, weight gain, and depression) are discussed, and data are presented that refute claims of the toxicity of tamoxifen therapy. From randomized controlled trials of adjuvant therapy, we know that tamoxifen therapy increases the rate of hot flashes, night sweats, and vaginal discharge; however, in observational studies these symptoms do not have a statistically significant impact on patients' quality of life as measured by standardized, self-report questionnaires. The Breast Cancer Prevention Trial found no evidence of excessive rates of depression or clinically significant differences in sexual functioning between women receiving placebo and those receiving tamoxifen therapy. Although several serious medical risks from tamoxifen therapy exist (e.g., uterine cancer, blood clots, stroke, and cataracts), there are additional benefits from tamoxifen therapy in addition to an increase in disease-free survival rates and overall survival rates, including a decrease in contralateral breast cancer and fractures. Ultimately, the decision to receive tamoxifen therapy is a personal choice for each woman to make on the basis of the evidence of tamoxifen therapy's benefits and risks, along with her own motivation to receive therapy. When the benefits of such therapy are small, some women may choose to avoid treatment, but others may wish to try therapy to determine whether possible side effects are relevant. For women in whom the absolute survival benefits are large, there may be less difficulty in making this decision. [J Natl Cancer Inst Monogr No. 30:2001;130–4]

Tamoxifen therapy has been an integral part of systemic adjuvant therapy since the early 1980s. This therapy was first used primarily in postmenopausal, lymph node-positive patients and subsequently in both premenopausal and postmenopausal patients with hormone receptor-positive, lymph node-negative tumors. More recently, tamoxifen therapy has been demonstrated to benefit women with noninvasive breast cancer and women at high risk for breast cancer. While the acute toxic effects of tamoxifen therapy are mild compared with combination chemotherapeutic regimens, concerns related to the side effects of this therapy have become more prominent with the increasing use of this agent in women with very early-stage disease [or women who are at high risk (1) only] where the absolute gains in survival are modest. If symptoms associated with a treatment are nearly universal, and the absolute benefit of the therapy is small, then one can begin to question the personal costs of such therapy. This is the current dilemma for women with very early-stage breast cancer who must decide whether or not to receive tamoxifen adjuvant therapy.

In this article, I will review the everyday symptoms and quality-of-life concerns associated with tamoxifen adjuvant therapy, the impact of tamoxifen on sexual functioning, the serious medical risks associated with the drug, and important considerations related to treatment decision-making about the use of tamoxifen therapy in the adjuvant setting. Ultimately, the decision to receive this therapy will rest with the patient; however, physicians are obligated to understand the benefits and risks of tamoxifen adjuvant therapy and to guide their patients in the decision-making process.

WHAT ARE THE EVERYDAY SYMPTOMS AND QUALITY-OF-LIFE CONCERNS ASSOCIATED WITH TAMOXIFEN ADJUVANT THERAPY?

After receiving a diagnosis of breast cancer and undergoing one or more of the various treatments prescribed to treat the disease (i.e., surgery, radiation therapy and adjuvant chemotherapy, or hormonal therapy), women have offered anecdotal reports of a range of symptoms that have been attributed to tamoxifen therapy, including weight gain, hair loss, joint pain, fatigue, depression, vaginal dryness, vasomotor symptoms (i.e., hot flashes and sweats), and diminished sexual functioning. Many of these symptoms are directly related to chemotherapy-induced menopause or to withdrawal of hormone replacement therapy; however, patients often attribute these symptoms to tamoxifen therapy, which is usually initiated subsequent to chemotherapy and hormone withdrawal. Furthermore, clinicians tend to remember very troubled patients, for whom the use of tamoxifen therapy seems to be associated with severe symptoms that have a major impact on quality of life, even though large numbers of their female patients tolerate this medication well and do not report changes in quality of life. In fact, many of the symptoms that have been attributed to tamoxifen therapy, such as vaginal dryness and weight gain, are now well-known to be concomitants of normal aging in women as they enter menopause (2,3).

It is important to move from anecdote to evidence as we consider the potential risks and side effects of tamoxifen adjuvant therapy. There are several good sources of data from descriptive longitudinal studies, cross-sectional comparison studies, and randomized controlled trials that use a placebo. Evidence from these studies will be used to discredit several myths about tamoxifen therapy as well as to document those symptoms that are increased in frequency as a result of this.

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therapy. Where available, data that examine the impact of symptoms on quality of life will also be described.

Does Adjuvant Tamoxifen Therapy Induce Premature Menopause?

There has been considerable interest in the risk of adjuvant chemotherapy inducing premature menopause (4), with limited prospective data available on this issue. Goodwin et al. (5) prospectively studied an inception cohort of 183 premenopausal women with locoregional breast cancer who received several forms of adjuvant therapy or no adjuvant treatment and followed up their status for 1 year to examine the predictors of the onset of menopause. No treatment was received by 29% of the sample; 12% received tamoxifen therapy alone; 45.3% received either cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or cyclophosphamide, epirubicin, and 5-fluorouracil (CEF); and 13.6% received either CMF or CEF followed by tamoxifen therapy. The multivariate model in this study included the following predictors: age, tumor size, lymph node status, chemotherapy, hormone therapy, and all relevant interaction terms. The final model found that age (<0.0001), chemotherapy (either CMF or CEF; <0.0001), and tamoxifen therapy (P = 0.034) were each statistically significantly and independently associated with the onset of menopause. The use of tamoxifen therapy in addition to either type of chemotherapy resulted in a small but statistically significant increase in the risk of menopause (4).

Goodwin et al. then went on to develop a model to predict the probability of the development of menopause according to age at diagnosis and type of adjuvant therapy (Fig. 1). The 95% confidence intervals for the chemotherapy and combined therapy curves overlap, as do the curves for tamoxifen therapy and no therapy. What this probability model demonstrates (Fig. 1) is that beyond the age of 35 years, the risk of menopause is statistically significantly increased when chemotherapy is used as opposed to tamoxifen therapy only or to no adjuvant therapy (5). These data provide important information for women who may be concerned about the risk of the onset of menopause associated with adjuvant therapy. While there may be some slight increased risk of premature menopause from tamoxifen therapy in the oldest group of premenopausal breast cancer patients, for women younger than 45 years of age, this is not a substantial risk. Even in older menstruating women, this model suggests that the incremental increased risk of menopause from tamoxifen therapy is only about 10% greater than in those women who receive no therapy (5).

Does Adjuvant Tamoxifen Therapy Cause Weight Gain?

Clinician and patient concern about weight gain after adjuvant chemotherapy have been noted for about two decades (6), and the same concern has been raised anecdotally about tamoxifen therapy, which has only recently been used more extensively in the adjuvant setting. Using a large inception cohort of 535 women with newly diagnosed locoregional breast cancer, Goodwin et al. (7) prospectively examined the question of weight gain after breast cancer. The mean age of the women in this study was 50.3 years, and 57% were premenopausal. The sample included patients with lymph node-negative and lymph node-positive tumors, as well as patients receiving no therapy, adjuvant tamoxifen therapy, or adjuvant chemotherapy. During 1 year of follow-up, 84.1% of the patients gained weight. In a multivariate analysis, the onset of menopause and the administration of chemotherapy were independent predictors of weight gain (all P < 0.05). Tamoxifen adjuvant therapy was not associated with an increased risk of weight gain (7).

Does Adjuvant Tamoxifen Therapy Contribute to Increased Symptoms or Diminished Quality of Life?

This question can be answered with data obtained in randomized trials as well as from a cross-sectional study of a large sample of breast cancer survivors. There are two randomized, placebo-controlled trials that have evaluated the toxicity of adjuvant tamoxifen therapy. In the Wisconsin Tamoxifen Trial conducted by Love et al. (8), 140 postmenopausal, lymph node-negative patients were randomly assigned to receive tamoxifen therapy or a placebo. With the use of an interviewer-administered questionnaire, patients were asked to evaluate their anxiety, a range of symptoms they had experienced, the overall toxicity of the therapy they had received, and their quality of life. Follow-up occurred during a 24-month period of time. Key findings from this study include an increase in hot flashes reported by women receiving tamoxifen therapy (67.2% versus 45.4% at 6 months; P < 0.01), with severe hot flashes reported by 20.3% of women receiving tamoxifen therapy versus 7.6% in those on placebo assessed at 6 months (P < 0.04), and more frequent occurrence of gynecologic symptoms (i.e., bleeding, irritation, or vaginal discharge) in those receiving tamoxifen therapy (29.7% versus 15.1% at 6 months; P < 0.05), and these were predominantly mild in severity (8). There were no differences between the two groups in reports of the symptoms of nausea, fatigue, bone pain, joint pain, racing heart, vomiting, depression, sweaty hands, irritability, difficulty sleeping, or gastrointestinal distress (8). Finally, there was no adverse effect on quality of life as measured by nonstandardized questionnaires.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial (9) in lymph node-negative, estrogen receptor-positive premenopausal and postmenopausal women provides a much larger double-blind, placebo-controlled trial sample for the consideration of this question (>1400 women were included in each treatment arm). However, no self-report data on symptoms or quality of life were obtained in this study. Nevertheless, detailed toxicity evaluation from the B-14 trial demonstrated a pattern of symptoms very similar to those found in the

![Fig. 1. Model of the estimated probability of developing menopause in the first year after being given a diagnosis of breast cancer according to type of adjuvant therapy received. Adapted with permission from (4).](https://academic.oup.com/jncimono/article-abstract/2001/30/130/936269)
Wisconsin Tamoxifen Trial (8). Over the course of 5 years of therapy in the NSABP B-14 trial (9), 64.1% of tamoxifen-treated patients reported hot flashes compared with 47.7% of placebo patients. Vaginal discharge was noted in 29.7% of tamoxifen-treated patients compared with 15.2% of placebo patients. There were no significant differences in reports of weight gain, weight loss, fluid retention, nausea and vomiting, or diarrhea. Protocol therapy was discontinued in an equal number of patients assigned to placebo and tamoxifen therapy; however, approximately 50% more patient withdrawals were attributed to treatment toxicity in the tamoxifen arm of the study (9).

In a recent cross-sectional study of symptoms and quality of life in breast cancer survivors an average of 3 years after breast cancer diagnosis, Ganz et al. (10) used state-of-the-art, self-report measures to evaluate these patients according to the type of adjuvant therapy that they received. Hot flashes and night sweats were reported statistically significantly more often by survivors who received adjuvant therapy (i.e., tamoxifen therapy, chemotherapy alone, or chemotherapy plus tamoxifen therapy) than by survivors who had not received any adjuvant therapy (<.0001), with rates of hot flashes in the tamoxifen-treated patients that were comparable to those noted in the placebo-controlled trials described earlier (8,9) (Fig. 2). The frequency of vaginal discharge was also increased among those survivors receiving adjuvant therapy (<.0001), with tamoxifen therapy making an important contribution to this increased rate of symptomatology (Fig. 2). Other symptoms (i.e., weight gain, forgetfulness, vaginal dryness, pain with intercourse, and difficulty concentrating) were not statistically significantly increased among those who had received tamoxifen adjuvant therapy (10). It is important that no statistically significant differences in quality of life or depressed mood could be attributed to the use of adjuvant tamoxifen therapy, in spite of statistically significant increases in vasomotor and vaginal symptoms (10).

The largest and most comprehensive assessment of symptoms and quality of life related to tamoxifen therapy comes from the recently completed Breast Cancer Prevention Trial (BCPT), a randomized, double-blind, placebo-controlled trial that included more than 13000 healthy, high-risk women (1,11). The BCPT used a battery of 104 items taken from standardized, self-report measures of quality of life, depressed mood, everyday problems (including menopausal symptoms), and sexual functioning (12). All participants were assessed before random assignment and at each follow-up visit (11,12). In a report from the first 11064 women who entered the trial and whose status had been followed up for 36 months, Day et al. (11) could not identify detrimental effects on quality of life or mood from tamoxifen therapy, although vasomotor symptoms and vaginal discharge were statistically significantly increased by the tamoxifen treatment. The side-effect profile of tamoxifen therapy varied somewhat across age groups, with hot flashes being most commonly reported in women in the 50–59 year age group (11).

Effect of Tamoxifen on Sexual Functioning

Research on healthy women and on women with breast cancer demonstrates an age-related decline in sexual functioning (13–15). In the BCPT (11), rates of sexual activity with a partner did not differ by tamoxifen therapy or placebo status, although a subtle decline in sexual activity was noted for both groups across the first 3 years of the randomized trial. However, tamoxifen-treated participants reported slightly increased rates of problems in sexual arousal and difficulty having orgasm (11). In cross-sectional studies by Ganz et al. (10,15) and by Meyerowitz et al. (16) of breast survivors, no statistically significant differences in sexual health and functioning were found in breast cancer survivors compared with healthy postmenopausal women. Furthermore, in a detailed study (17) of the predictors of sexual health after breast cancer, chemotherapy treatment was the only statistically significant treatment-related variable predicting sexual dysfunction, and it was associated with a greater risk of vaginal dryness, a symptom that is usually not related to tamoxifen therapy.

Serious Medical Risks of Tamoxifen Therapy

In considering whether or not to take adjuvant tamoxifen therapy, many women with small tumors in the breast weigh heavily the other potential adverse consequences of tamoxifen therapy, such as strokes, blood clots, cataracts, and endometrial cancer (1,18–21). Although the relative reduction in risk of breast cancer systemic recurrence is uniform across all stages of the disease, the absolute benefit decreases relative to disease burden (Fig. 3). As suggested by the examples in Fig. 3, a woman with a very limited tumor burden (e.g., patient A with a 1-cm tumor, negative lymph nodes, and positive hormone receptors) will benefit from tamoxifen adjuvant therapy independent of her age, but she will have a variable risk of side effects (serious medical events or symptoms) based on her age. For a 43-year-old woman with a disease burden equivalent to patient A, the benefits of tamoxifen therapy in terms of decreased recurrence, overall survival, and breast cancer risk reduction in the contralateral breast will likely outweigh the potential for side effects. However, a 75-year-old woman with the same degree of tumor burden may choose to avoid tamoxifen adjuvant therapy because of her higher risk for adverse medical events or side effects. In contrast, all women with a disease burden equivalent to patient C, independent of age, will perceive an increased benefit from tamoxifen adjuvant therapy in spite of variable side-effect profiles.

The competing adverse risks and side effects of tamoxifen adjuvant therapy must be balanced against the potential gains in
Weighing the Risks and Benefits: A Personal Choice

The presentation of information to patients about the benefits and risks of tamoxifen adjuvant therapy is complex. Although the relative benefits of this therapy are equally distributed across all ages and tumor stages, the absolute benefits gained for an individual woman are strongly influenced by her disease burden. The question, simply stated, is: How much absolute benefit is required before one should consider taking adjuvant therapy? From a societal perspective, we may ask: How many women must benefit from a treatment before a recommendation can be made that all such women at risk should take the treatment? Furthermore, is survival the only meaningful end point, or is disease-free survival more important for some women? In addition, we must ask about the burden to the patient of taking a medication daily for 5 years that may cause troublesome vaso-motor symptoms or vaginal discharge. Does the patient see enough value in increased survival, disease-free survival, or the prevention of a second cancer to offset these symptoms? Finally, does tamoxifen adjuvant therapy also provide some reassurance and sense of protection for women who feel psychologically vulnerable as a result of having been diagnosed with cancer?

Ultimately, the individual woman’s perception of benefits and risks, as well as her personal motivation to do something to combat the disease, are the strongest influences in the decision-making process. However, it is important to realize that this treatment can always be discontinued if the woman determines that she has made the wrong decision. In essence, the use of tamoxifen adjuvant therapy in each woman is an “n of 1” trial, where we will never know with certainty whether the absence of recurrence is the result of this therapy. With careful clinical monitoring, we can assess the actual likelihood of side effects in the individual woman and can either continue or discontinue therapy based on the patient’s preference after a trial of the medication.

The challenge to the physician prescribing tamoxifen adjuvant therapy is to understand fully the magnitude of benefits, risks, and side effects of this treatment and to be able to communicate this information effectively to the patient. It is critical to respect the woman’s personal preferences and choices. Furthermore, physicians should be gracious about discontinuing this therapy if the patient believes the side effects outweigh the benefits after she has undergone a therapeutic trial of tamoxifen.

Conclusions

The major symptoms attributable to tamoxifen therapy experienced by women taking this form of adjuvant therapy are hot flashes, sweats, and vaginal discharge. Other common symptoms associated with aging and menopause, such as joint pain, weight gain, changes in mood, and difficulty concentrating, cannot be directly ascribed to the use of tamoxifen therapy but are more likely the result of estrogen deficiency associated with menopause. It is important that tamoxifen adjuvant therapy does not appear to statistically significantly increase the risk of menopause onset in premenopausal women (4). There is no evidence to support poorer quality of life or an increased risk of depression in women who receive tamoxifen as adjuvant therapy after breast cancer (11). These conclusions are derived, however, from the averaging of data from many women, and some individuals within these groups may have adverse experiences. Sexual functioning after breast cancer is adversely affected by the presence of vaginal dryness, which is not a specific side effect of tamoxifen therapy but is probably the result of age-related estrogen deficiency and adjuvant chemotherapy treatment (15,17).

REFERENCES


NOTE

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