Drug Therapy

ALASTAIR J.J. WOOD, M.D., *Editor*

TAMOXIFEN IN THE TREATMENT OF BREAST CANCER

C. KENT OSBORNE, M.D.

BREAST cancer is the most common cancer in women in the Western world. Because breast cancer is estrogen-dependent, reducing estrogen secretion by oophorectomy, hypophysectomy, or adrenalectomy can cause the cancer to regress. The need for these surgical procedures was reduced by the introduction of tamoxifen, which acts as an antiestrogen by inhibiting the binding of estrogen to estrogen receptors. Tamoxifen was approved by the Food and Drug Administration in 1977 for the treatment of women with advanced breast cancer and several years later for adjuvant treatment of primary breast cancer.[1]

PHARMACOLOGY AND ENDOCRINOLOGY

Pharmacologic and Pharmacokinetic Properties

The compound administered to patients is *trans*-tamoxifen (as the citrate salt), because this isomer has higher affinity for estrogen receptors than the cis isomer.[2] These receptors are nuclear transcription factors present in normal breast and other tissues and in 60 to 70 percent of breast cancers. The *trans*-tamoxifen has not only antiestrogenic but also estrogenic properties, depending on the species, tissue, and gene.[3] Drugs such as tamoxifen are more properly referred to as selective estrogen-receptor modulators, because of their multiple activities.[4] The molecular basis for these properties is poorly understood, but the estrogen-agonist activity of tamoxifen may explain its favorable effects on bone and serum lipid concentrations and its ability to stimulate the endometrium. Its estrogen-antagonist activity in breast tissue accounts for its ability to inhibit tumor growth.

The major metabolites of tamoxifen in humans are *N*-desmethyltamoxifen and *trans*-4-hydroxytamoxifen (Fig. 1); the affinity of the latter for estrogen receptors is equivalent to that of 17β-estradiol.[5] The dimethylaminoethoxy side chain and the trans configuration are crucial for the antiestrogenic activity of tamoxifen[2,5]; more highly estrogenic cis metabolites and metabolites without the side chain have been found in breast tumors, but their importance is unclear.[6]

Tamoxifen is absorbed readily after oral administration.[2,5] The serum half-lives of tamoxifen and its major metabolites range from 7 to 14 days, permitting once-daily administration.[2,5,7] The usual dosage is 20 mg per day.[8] In long-term treatment, the steady-state concentrations of tamoxifen and its metabolites in serum remain constant for as long as 10 years; reduced bioavailability is not a cause of acquired resistance to the drug.[9] Tamoxifen can be detected in serum for several weeks and in tumor tissue for several months after treatment is discontinued.[7] As a result, for several months after tamoxifen treatment is stopped, ligand-binding assays of estrogen receptors in tumor tissue can give false negative results because of receptor occupancy by the drug.[10,11] Tamoxifen undergoes extensive metabolism in the liver and is excreted predominantly in the feces.

Serum tamoxifen concentrations vary widely from patient to patient.[2,5] Treatment responses, however, do not correlate with steady-state serum concentrations of the drug, and doses greater than 20 mg daily are not more effective than this dose.[12-16]

Tamoxifen increases the action of warfarin by competing with its metabolizing enzyme, cytochrome P450 3A4, a circumstance that can lead to potentially life-threatening bleeding.[17] Therefore, patients receiving tamoxifen should be given less warfarin, and the international normalized ratio should be closely monitored. Erythromycin, cyclosporine, nifedipine, and diltiazem can inhibit tamoxifen metabolism by a similar mechanism.[18]

Endocrine Effects

Postmenopausal women have very low serum estrogen and progesterone concentrations and high serum luteinizing hormone and follicle-stimulating hormone concentrations. In these women, tamoxifen reduces gonadotropin secretion.[19-21] In premenopausal women it slightly increases gonadotropin and estrogen secretion.[20-22] An increase in endogenous estrogen secretion might be expected to displace tamoxifen from estrogen receptors and therefore limit its therapeutic efficacy. However, the similar survival benefits of tamoxifen in women both before and after menopause argue against this possibility.[23]

Mechanism of Action

The antitumor effects of tamoxifen are thought to be due to its antiestrogenic activity, mediated by competitive inhibition of estrogen binding to estrogen receptors.[3] As a consequence, tamoxifen inhibits the expression of estrogen-regulated genes, including growth factors and angiogenic factors secreted by the tumor that may stimulate growth by autocrine

From the Department of Medicine, Division of Medical Oncology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr., San Antonio, TX 78284-7884, where reprint requests should be addressed to Dr. Osborne.

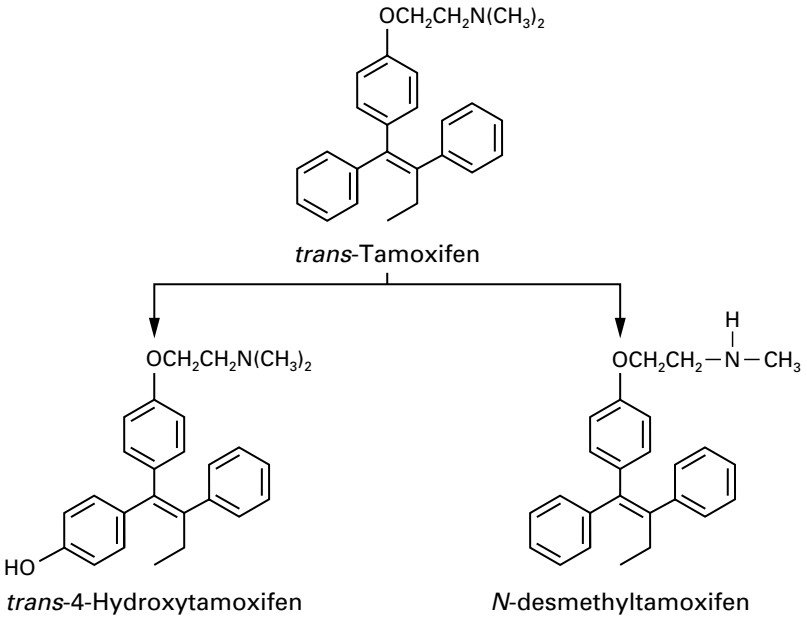

Figure 1. The Structures of Tamoxifen and Its Major Metabolites in Humans.

or paracrine mechanisms.[24] The net result is a block in the G1 phase of the cell cycle and a slowing of cell proliferation. Tumors may then regress because of this altered balance between cell proliferation and ongoing cell loss. Tamoxifen may also directly induce programmed cell death.[25]

ADJUVANT TREATMENT OF BREAST CANCER

Most women presenting with a new diagnosis of breast cancer have stage I disease (a tumor less than 2 cm in diameter with histologically negative axillary nodes) or stage II disease (a tumor as large as 5 cm with either negative or positive nodes). Some women present with locally advanced stage III disease, but fewer than 10 percent have clinically detectable distant metastases (stage IV) at the initial diagnosis. However, clinically undetectable micrometastases are present in many women with stage I and, especially, stage II disease. These women usually have a recurrence and die of their disease if they are not given effective systemic adjuvant treatment (treatment administered after surgery for breast cancer in an attempt to eradicate the micrometastases). Others, especially those with no tumor involvement of the axillary lymph nodes, do not have viable micrometastases, and their disease can be cured by surgery alone.

It is difficult to distinguish cases in which surgery is curative from those involving micrometastases, and therefore many women who do not really need adjuvant therapy receive it. Nevertheless, postoperative therapy with tamoxifen reduces the risk of recurrence and prolongs survival in women with operable breast cancer in whom the tumors are confined to the breast or axillary lymph nodes.[23] It is most beneficial in women whose tumors contain estrogen receptors and in those who are given the drug for about five years.

The level of estrogen receptors should be measured in all cases of breast cancer. This is usually done by means of a ligand-binding assay, enzyme immunoassay, or immunohistochemical analysis. The interpretation of data on estrogen receptors is complicated by the lack of consistency among the cutoff values chosen by laboratories to define an estrogen-receptor–negative result. Some laboratories designate tumors with detectable but low concentrations of estrogen receptors as negative, which may explain why tamoxifen was found to be beneficial in women with "estrogen-receptor–negative" tumors in some trials (see below). Other data suggest that tumors with any detectable level of estrogen receptors — with even 1 percent of cells staining positive — should be considered positive.[26,27] Similarly, using immunohistochemical analysis, some laboratories include tumors in which 10 or even 20 percent of the cells contain estrogen receptors among those designated estrogen-receptor–negative. Unless those laboratories have justified their cutoff values with clinical follow-up data, many women may be misclassified as having estrogen-receptor–negative tumors and thus may not be offered potentially beneficial tamoxifen treatment. Physicians need to know how their labo-

ratories measure estrogen receptors in tumors and how negative and positive values are defined.

Because progesterone receptors are regulated by estrogen, the estrogen-receptor–negative, progesterone-receptor–positive phenotype would not be expected to occur frequently, and in fact only 5 percent of tumors are of this type. Some of these cases represent false negative findings on estrogen-receptor assays, and given the relatively high response rate of such tumors to tamoxifen, women with these tumors should be considered good candidates for tamoxifen therapy despite the apparent absence of estrogen receptors in the tumor tissue. Measurement of progesterone receptors by the same techniques as those used to measure estrogen receptors is also helpful in selecting women for hormonal therapies such as tamoxifen. In cases of metastatic breast cancer, the presence of progesterone receptors indicates a greater likelihood of a response to tamoxifen than their absence, but a finding of progesterone receptors is less useful in selecting women for adjuvant therapy with the drug.[23]

Ductal Carcinoma in Situ

Women with ductal carcinoma in situ (intraductal cancer) have a very low risk of death from the disease, because, by definition, the cancer has not yet spread beyond the duct.[28] Systemic therapy is not indicated for these women; they should be treated by simple mastectomy or by lumpectomy with or without breast irradiation. Ongoing studies are evaluating tamoxifen to reduce the recurrence of ipsilateral or contralateral breast cancer in such patients.

Invasive Breast Cancer

More than 37,000 women with operable breast cancer were enrolled in 55 randomized clinical trials of adjuvant therapy with tamoxifen before 1990, providing a large data base of findings on long-term follow-up. The results of these studies were summarized recently in an update of a meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group.[23]

When all the women and all the durations of treatment were included in the analysis, tamoxifen was found to be associated with a significant reduction in recurrence and death after a median follow-up of about 10 years. The annual reductions in recurrence and death with tamoxifen as compared with placebo were 26 and 14 percent, respectively. This means that each year, about one of every four recurrences and one of every six deaths can be delayed or averted with tamoxifen treatment. The gains are substantially greater in women with tumors expressing estrogen receptors and in women treated for five years.[23]

Estrogen-Receptor Status

Whether tamoxifen improves outcomes in women who have tumors with few or no estrogen receptors has been controversial. It has little or no effect on estrogen-receptor–negative tumor cells in culture or on tumors in animals.[29,30] Furthermore, responses are uncommon (5 to 10 percent) in women with estrogen-receptor–negative metastatic breast cancer treated with the drug.[31] The results of large trials of adjuvant therapy in women with estrogen-receptor–negative tumors were contradictory.[32-34] A 1992 meta-analysis of trials of adjuvant therapy suggested that tamoxifen has a small but statistically significant survival benefit in these women,[35] but the updated meta-analysis with longer follow-up and additional women did not (Table 1).[23]

For women with estrogen-receptor–positive tumors, tamoxifen therapy given for as little as one year results in a statistically significant recurrence and survival benefit. The benefits increase as the duration of treatment increases, so that among women treated for five years, tamoxifen results in a 50 percent annual reduction in the recurrence rate and a 28 percent annual reduction in the death rate. This means that about half of the recurrences and more than one fourth of the deaths each year are averted by tamoxifen treatment. The benefits are even greater in women whose tumors have very high concentrations of estrogen receptors. Relatively few studies have included measurements of progesterone receptors in tumor tissue. Among women with estrogen-receptor–positive tumors, the efficacy of tamoxifen was independent of the concentration of progesterone receptors in the tumor tissue.[23] Among women with estrogen-receptor–negative tumors, those whose tumors contained progesterone receptors did benefit from tamoxifen.

TABLE 1. META-ANALYSIS OF TRIALS OF ADJUVANT TAMOXIFEN THERAPY IN WOMEN WITH BREAST CANCER, ACCORDING TO ESTROGEN-RECEPTOR STATUS AND DURATION OF THERAPY.*

DURATION OF TAMOXIFEN THERAPY	NO. OF WOMEN†	NO. OF EVENTS AVERTED EACH YEAR	
		RECURRENCE	DEATH
One year			
ER-negative	1591	0‡	0‡
ER-positive	3352	1 in 5	1 in 7
Two years			
ER-negative	5145	0‡	0‡
ER-positive	8635	1 in 3 or 4	
Five years			
ER-negative	922	0‡	0‡
ER-positive	5869	1 in 2	1 in 3 or 4

*Data are from the Early Breast Cancer Trialists' Collaborative Group.[23] ER denotes estrogen receptor.

†The numbers of women shown are those who participated in the trials comparing tamoxifen with no tamoxifen.

‡The data cannot exclude the possibility that occasionally a woman might benefit.

Optimal Duration of Therapy

Preclinical studies suggest that tamoxifen is primarily a cytostatic agent and therefore that prolonged therapy would be more effective than short periods of treatment.[36] In the most recent meta-analysis, comparisons of the results of trials of about one, two, and at least five years' duration (Table 1) suggest that in women with estrogen-receptor–positive tumors, prolonged therapy (about five years) is superior to shorter therapy in reducing the rates of recurrence and death.[23,35]

Several recently completed trials compared different durations of treatment directly. In two large European trials, women treated with tamoxifen for five years had fewer recurrences and fewer deaths than those treated for two years.[37,38] Two North American trials, one large and one small, compared tamoxifen treatment lasting 5 years with treatment lasting about 10 years,[39-41] and a trial in Scotland compared 5 years with indefinite tamoxifen treatment.[42] Although the follow-up periods were short and thus the numbers of recurrences and deaths were small, there was no convincing evidence that treatment lasting longer than five years was beneficial. In addition, in two of these trials there was a trend toward a detrimental effect after treatment for more than five years.[40,42] On the basis of these results, it now seems reasonable to recommend that tamoxifen be given for five years.

Benefits According to Age or Menopausal Status

The 1992 meta-analysis suggested that tamoxifen had no benefit in younger women.[35] However, many women with estrogen-receptor–negative tumors were included in the studies, and the duration of treatment was usually only one or two years. There is now considerable evidence suggesting that more prolonged treatment results in significant benefit in women less than 50 years old and in older women with estrogen-receptor–positive tumors. In a large, five-year, placebo-controlled trial in women with estrogen-receptor–positive tumors whose lymph nodes contained no tumor, tamoxifen was more effective than placebo both in women who had reached menopause and those who had not.[39,40] The recent meta-analysis confirmed these results (Table 2).[23] Women less than 50 years old, most of whom would be expected to be premenopausal, benefit from tamoxifen as much as older women, and even women younger than 40 have reduced rates of recurrence and death. These data suggest that tamoxifen inhibits the proliferation of breast-cancer cells even in the presence of estrogen.

An important question is whether the benefit of tamoxifen therapy is equivalent to or greater than that of chemotherapy in premenopausal women, as it appears to be in older women who have estrogen-receptor–positive tumors. Although the data in Table 2 suggest that tamoxifen is at least as effective as adjuvant chemotherapy in women younger than 50 (chemotherapy was associated with a 36 percent reduction in the recurrence rate and a 24 percent reduction in the death rate),[35] few studies have directly addressed this question. In a single small study of premenopausal women with metastases to the lymph nodes and primary tumors containing estrogen receptors, chemotherapy was superior to tamoxifen, but the duration of tamoxifen treatment was only two years.[43] In a large, randomized trial comparing tamoxifen alone with chemotherapy plus tamoxifen, the combination was more effective.[44]

TABLE 2. META-ANALYSIS OF RESULTS OF ADJUVANT TAMOXIFEN THERAPY FOR FIVE YEARS IN WOMEN WITH ESTROGEN-RECEPTOR–POSITIVE BREAST CANCER, ACCORDING TO AGE.*

AGE (YR)	NO. OF WOMEN†	NO. OF EVENTS AVERTED EACH YEAR	
		RECURRENCE	DEATH
<40	1327	1 in 2 or 3	1 in 3 or 4
40–49	1327	1 in 2 or 3	1 in 3 or 4
50–59	2536	1 in 2 or 3	1 in 3 or 4
60–69	3174	1 in 2 or 3	1 in 3 or 4
≥70	390	1 in 2 or 3	1 in 3 or 4

*Data are from the Early Breast Cancer Trialists' Collaborative Group.[23]

†The numbers of women shown for each age group are those who participated in the trials comparing tamoxifen with no tamoxifen.

Benefits in Women with and Women without Metastases to the Axillary Lymph Nodes

Many of the early trials of adjuvant tamoxifen focused on the treatment of women with node-positive disease. However, one of the largest studies of adjuvant tamoxifen therapy included more than 2600 women who had estrogen-receptor–positive tumors but no nodal disease and who were given tamoxifen or placebo for five years.[39,40] There were significantly fewer recurrences and deaths in both premenopausal and postmenopausal women given tamoxifen for five years than in those given placebo. The updated meta-analysis also demonstrates similar reductions in the rates of recurrence and death in both women with node-negative cancers and those with node-positive cancers.[23]

Benefits in Elderly Women

In many older women, the presence of concurrent systemic disease complicates the identification of optimal local and systemic treatments. However, tamoxifen is beneficial in women 70 years of age or older (Table 2).[23,45] The reductions in the rates of recurrence and death are substantial, and these women tolerate the drug well. It should be emphasized that in elderly women, tamoxifen is not an adequate substitute for definitive surgical treatment.

Tamoxifen in Combination with Adjuvant Chemotherapy

Because of the benefits both of adjuvant tamoxifen and of adjuvant chemotherapy, trials were initiated to assess the benefits of these two treatments given together. In premenopausal women, most trials in which chemotherapy plus tamoxifen was compared with chemotherapy alone revealed that combination therapy offers little additional benefit.[35,46-49] However, many of these trials included women with tumors that were estrogen-receptor–negative or whose estrogen-receptor status was unknown, and in many cases tamoxifen was given for only one or two years. In an analysis of five-year data on women with estrogen-receptor–positive tumors, tamoxifen plus chemotherapy was superior to the same chemotherapy given alone, not only in women 50 years old or older but also in younger women.[23]

Given the established benefits of tamoxifen in postmenopausal women, deciding whether to add chemotherapy to tamoxifen is an important issue. Some trials showed a small reduction in the rate of recurrence, but in only one trial of chemotherapy (doxorubicin and cyclophosphamide) plus tamoxifen was there a survival benefit with combined treatment.[50-55] In two other trials, one in women with node-negative tumors and another in women with node-positive and estrogen-receptor–positive tumors, the rates of recurrence were lower in the women receiving chemotherapy plus tamoxifen, but there has been no difference in survival.[44,56] Given the advantage in terms of disease-free survival found in the 1992 meta-analysis and in several large individual trials[35] and the survival benefit reported in the study of doxorubicin plus cyclophosphamide,[54] an argument can be made for treating higher-risk postmenopausal women with both chemotherapy and tamoxifen. Given the limited therapeutic gains, however, the additional toxicity associated with chemotherapy should be considered when treatment decisions are made.[57]

TREATMENT OF METASTATIC BREAST CANCER

Women with clinically evident metastatic disease also benefit from tamoxifen treatment. Women with indolent disease (a disease-free interval lasting more than two years after initial surgery; soft-tissue, bone, or nodular lung metastases; and estrogen or progesterone receptors) have the best response to tamoxifen (Fig. 2). These women are treated sequentially with secondary and tertiary endocrine therapies until their tumors no longer respond. Chemotherapy is then indicated. Women with more rapidly advancing disease are usually treated initially with chemotherapy, especially if the tumor does not contain estrogen receptors. Overall, about 30 percent of women with metastatic breast cancer treated with tamoxifen had objective regression of the tumor for an average of 12 months, and in another 20 percent the disease remained stable for at least 6 months.[58] About half of all women with estrogen-receptor–positive tumors receive some benefit from tamoxifen, as compared with only 5 percent of women with tumors in which estrogen receptors cannot be detected. A few women have remissions lasting more than five years, but resistance to tamoxifen inevitably develops.

A prospective study of nearly 400 women demonstrated that menopausal status and the presence or absence of estrogen or progesterone receptors determined whether the disease would respond well to tamoxifen.[59] Premenopausal women with estrogen-

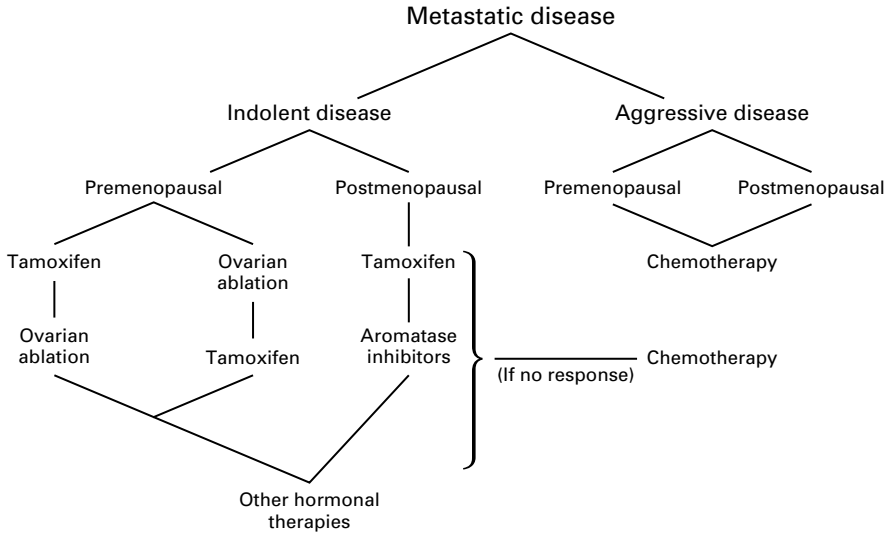

Figure 2. Approach to the Treatment of Women with Metastatic Breast Cancer.

receptor–positive tumors had an overall response rate of only 24 percent, as compared with an 86 percent response rate among postmenopausal women whose tumors were strongly positive for estrogen and progesterone receptors. Women with estrogen-receptor–positive, progesterone-receptor–negative tumors had a lesser but still significant and clinically substantial benefit.

Small, randomized trials in premenopausal women have suggested that tamoxifen offers treatment benefits similar to those achieved with oophorectomy.[60,61] In addition, tamoxifen can be effective as a second-line endocrine therapy after oophorectomy, and vice versa. In postmenopausal women with metastatic disease, including women in whom there is a relapse of disease six months or more after the discontinuation of adjuvant therapy with tamoxifen, tamoxifen is the initial endocrine therapy of choice.[62] In postmenopausal women, tamoxifen therapy is similar in benefit to adrenalectomy, hypophysectomy, and diethylstilbestrol treatment.[63-66] Tamoxifen may be slightly superior to standard-dose progestin therapy.[67] In one study, high-dose progestin therapy had a response rate that was superior to that with tamoxifen, but survival was not longer and toxicity was greater.[68] Combinations of tamoxifen with other endocrine therapies, such as progestins, or with cytotoxic chemotherapy do not confer any greater survival advantage than sequential therapy.[69-71] An exception may be the combination of tamoxifen and goserelin in premenopausal patients.

TREATMENT OF MEN WITH BREAST CANCER

Breast cancer is uncommon in men, but the usual approach to treatment parallels that in women. Growth of breast cancer in men is regulated partially by sex steroid hormones, both androgens and estrogens, and a high percentage of men with the disease benefit from ablative or additive endocrine therapies.[72] Eighty to 90 percent of their tumors contain estrogen receptors, nearly 7 percent contain progesterone receptors, and 50 percent contain androgen receptors.[73-75] This high degree of receptor expression is associated with a high rate of response to hormonal therapies such as orchiectomy or tamoxifen, which are the preferred treatments. Because of the rarity of the disease, no large trials of adjuvant tamoxifen or chemotherapy in men with breast cancer have been conducted, but several small, nonrandomized studies suggest that adjuvant therapy increases survival.[74,76] Tamoxifen often induces remissions in men with metastatic disease whose tumors express estrogen receptors,[77] either as an initial therapy or after orchiectomy. Because of the lower degree of acceptance of surgical orchiectomy by men, tamoxifen has become the most frequently used hormonal therapy in men with breast cancer.[78]

TABLE 3. POSSIBLE CAUSES OF TAMOXIFEN RESISTANCE.

Absence or loss of estrogen receptors
Noncompliance with treatment regimen
Tamoxifen-stimulated growth of tumor
Variant or mutant estrogen receptors
Altered expression of receptor-interacting proteins
Cross-talk among growth factor signaling pathways

Men with breast cancer may not tolerate tamoxifen as well as women. In one study, 20 percent of the men stopped treatment because of decreased libido, hot flashes, mood changes, and deep venous thrombosis.[78] Nevertheless, tamoxifen is an effective treatment in men with breast cancer.

RESISTANCE

New or acquired resistance limits the efficacy of tamoxifen in many patients with breast cancer (Table 3). Some have tumors that spontaneously become hormone-independent despite the presence of estrogen receptors; in others, tumors that are initially estrogen-receptor–positive become estrogen-receptor–negative over time.[10,11] Yet at least two thirds of the tumors that become resistant to tamoxifen continue to express estrogen receptors, and many of these regress when second-line hormonal therapy is initiated.[11,58,61,63]

In at least some patients the disease progresses during tamoxifen therapy because tumor growth is stimulated by it.[79] Tamoxifen-stimulated growth explains the "withdrawal response" that occurs in some patients when the drug is stopped because of tumor progression, and it explains the lack of response to oophorectomy in premenopausal women if tamoxifen is not discontinued at the time tumor progression is observed.[79] Possible mechanisms of this type of tamoxifen resistance include the presence of variant estrogen receptors, altered expression of other transcription factors that interact with estrogen receptors and modify their activity, and "cross-talk" among estrogen receptors and other growth-factor signal-transduction pathways (Table 3).[3,4,79] Tamoxifen should be discontinued when evidence of tumor progression becomes clear. Noncompliance may explain a few cases of apparent drug resistance.

ANCILLARY BENEFITS

Serum Lipoproteins and Mortality from Cardiovascular Causes

In women with breast cancer, tamoxifen does not reduce the incidence of non–cancer-related deaths.[23]

However, accurate data on causes of death are difficult to obtain in some countries, and several individual trials of adjuvant therapy did suggest that the rate of non–breast-cancer-related deaths (deaths before relapse) may be reduced by tamoxifen treatment.[33,80-82] This reduction appears to be due largely to a decrease in deaths from cardiovascular causes. In addition, fewer hospitalizations for cardiac events have been reported among women taking tamoxifen.[81] The estrogenic properties of tamoxifen may account for these reductions.[81,83,84] Serum concentrations of total cholesterol and low-density lipoprotein cholesterol are reduced by tamoxifen, which may also inhibit atherogenesis by directly affecting the metabolism of low-density lipoproteins in the arteries.[85]

Changes in Bone Mineral Density

In postmenopausal women, long-term tamoxifen treatment slightly increases the bone density of the axial skeleton and stabilizes the bone density of the appendicular skeleton.[86,87] In premenopausal women, however, tamoxifen may decrease bone mineral density, perhaps by antagonizing the more potent activity of endogenous estrogen.[88] Despite the apparently favorable effects of tamoxifen on bone density in postmenopausal women, in a one-year study the fracture rate was higher in women treated with tamoxifen than in those given placebo.[89] However, the fracture rate seems to be reduced with five years of treatment (see below).

Prevention of Contralateral Breast Cancer and of Breast Cancer in Women at High Risk

Tamoxifen reduces the incidence of cancer in the contralateral breast. Individual trials in women with invasive breast cancer as well as the updated meta-analysis from the Early Breast Cancer Trialists' Collaborative Group indicated that there is a nearly 50 percent reduction in the risk of contralateral cancer after about five years of treatment.[23,40,90-92] These results provided the rationale for the current trials assessing tamoxifen for the prevention of breast cancer in women at high risk for the disease. Preliminary results of one of these studies, a prevention trial of long-term tamoxifen therapy in the United States, involving over 13,000 women at increased risk for breast cancer, are encouraging. After a mean of 3.6 years, the incidence of breast cancer was 45 percent lower in the group receiving tamoxifen (85 cases of cancer) than in the group receiving placebo (154 cases).[93] The incidence of fractures was lower and that of endometrial cancer was higher in the tamoxifen group; there was no significant difference between the two groups in the incidence of ischemic heart disease. According to these findings, tamoxifen for prevention might be considered for women at high risk, but extrapolation of the results to other women is unwarranted.

TOXICITY

Tamoxifen is extremely well tolerated by most patients with breast cancer. In early trials of tamoxifen for adjuvant therapy, fewer than 5 percent of patients withdrew from therapy because of toxicity.[33,94] In a more recent, large, randomized trial, 7 percent of tamoxifen-treated women withdrew for reasons apparently related to drug toxicity, but 5 percent of placebo-treated women also withdrew for those reasons.[39,40]

Menopausal Symptoms

The most common adverse effects of tamoxifen are menopausal symptoms, and they are more common in women before menopause than afterward (Table 4).[39,40,95] At least 50 percent of women treated with tamoxifen report hot flashes, but so do 20 to 40 percent of women given placebo. Many of these women have recently stopped estrogen-replacement therapy, at the time the diagnosis of breast cancer was made. Vaginal discharge and irregular menses are also slightly more common among women treated with tamoxifen than among those given placebo. However, in one study, the incidence of nausea, discomfort in the joints, difficulty sleeping, restlessness, depression, or fatigue was similar in the tamoxifen and placebo groups, and headache was less common in the tamoxifen group.[95] Quality-of-life scores were similar in the two groups.

Ocular, Thromboembolic, and Hematologic Effects

Retinopathy has been reported in women given high doses of tamoxifen,[96] but reports of ocular toxicity with conventional doses in randomized trials are inconsistent.[97-100] In one large trial and in preliminary results from the tamoxifen prevention trial, no vision-threatening toxic effects were found, but among women with preexisting cataracts there was a slightly increased risk of posterior subcapsular opacities and a slightly increased need for cataract surgery in those receiving tamoxifen.[100]

An increased incidence of thromboembolic phenomena has also been attributed to tamoxifen in some

TABLE 4. ADVERSE EFFECTS OF TAMOXIFEN.

Menopausal symptoms
Hot flashes
Atrophic vaginitis
Irregular menses
Ocular toxicity
Thromboembolic events
Thrombocytopenia or leukopenia
Gynecologic complications
Endometrial cancer (low grade)
Endometrial hyperplasia and polyps
Ovarian cysts

but not all studies, especially when tamoxifen is combined with chemotherapy.[32,33,39,81,101,102] This complication occurs in fewer than 1 percent of patients given tamoxifen, but deaths due to thromboembolism have been reported.[39] Many of the patients described had superficial phlebitis and did not require hospitalization. Moderate thrombocytopenia and leukopenia have been reported with tamoxifen, but they rarely require cessation of therapy.

Endometrial Cancer

The most serious adverse effect of tamoxifen is its potential tumor-promoting activity. Electrophilic metabolites can form covalent DNA adducts.[103] An increased incidence of liver tumors has been reported in rats,[104] but only a few cases of hepatoma have ever been reported in humans taking tamoxifen.[91,92,105] More serious is an increased incidence of endometrial cancer, similar to that in women receiving estrogen-replacement therapy; it has been reported in some but not all tamoxifen trials and may be related more to tamoxifen's estrogenic activity than to any direct carcinogenic effects.[91,92,106-109] Nearly all reported endometrial cancers have been in postmenopausal women. In a large five-year trial of tamoxifen, the annual hazard rate was 1.7 per 1000 women, a relative risk of 2.2 as compared with population-based rates of endometrial cancer.[106] Most of the cancers were of a low stage and grade, similar to those associated with estrogen therapy. In the most recent meta-analysis, the incidence of endometrial cancer was increased and the risk of mortality from endometrial cancer was slightly increased, especially with prolonged treatment.[23]

Endometrial hyperplasia, the development of polyps, an increase in endometrial thickness, and ovarian cysts have also been attributed to tamoxifen.[92,110,111] The value of routine screening for endometrial cancer in women receiving tamoxifen has not been established, but certainly any woman with unusual vaginal discharge or bleeding should be promptly evaluated. The large prospective trials of tamoxifen did not find a significantly increased incidence of other solid tumors,[23,90-92,106,107] and the reduction in the incidence of contralateral breast cancer (a more lethal disease) is about twice as large as the increase in the incidence of endometrial cancer.[23]

CONCLUSIONS

Tamoxifen reduces the risk of recurrence and death from breast cancer when given as adjuvant therapy, and it provides effective palliation for patients with metastatic breast cancer. Its use is therefore indicated for both premenopausal and postmenopausal women who have estrogen-receptor–positive invasive breast cancer. An exception might be women considered — on the basis of prognostic factors, such as an invasive tumor no more than 1 cm in diameter, or tubular, mucinous, or papillary tumors with negative axillary nodes — to have a very low risk of disseminated disease. Tamoxifen is also the initial hormonal therapy of choice for postmenopausal women with metastatic breast cancer, and it is useful as first- or second-line therapy in younger women. It is safe and well tolerated, but the risk of endometrial cancer is increased. The possible beneficial effects of tamoxifen on cardiovascular mortality, bone density, and the risk of contralateral breast cancer are added benefits that justify the ongoing prevention trials in women at high risk for the development of breast cancer.

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