Breast cancer treatment has evolved greatly within the last 25 years. Tamoxifen was first introduced for the

Introduction

Tamoxifen (Nolvadex) is an effective, well-tolerated drug that can benefit breast cancer patients by increasing survival, both overall and disease-free, and reducing the risk of contralateral breast cancer. Tamoxifen has some important secondary benefits such as decreasing lipid levels, reducing cardiovascular risk, and preventing a decrease in bone mineral density, all of which may be important factors in selection of treatment. As with most drugs, tamoxifen is associated with side effects; however, tamoxifen is a well-tolerated drug--less than 1% of patients discontinue its use due to side effects.

It is important that balanced information on the risks and benefits of tamoxifen be communicated to patients, preferably with information on absolute risks and benefits. For the breast cancer patient, the benefits of tamoxifen clearly outweigh the risks.

Over many years as clinicians, we have seen the impact of tamoxifen in three different settings: metastatic breast cancer, adjuvant therapy, and preventive therapy. The purpose of this article is to describe[]from the oncologists' perspective[]the evolution of breast cancer therapy over the years, with a focus on tamoxifen.

Metastatic Breast Cancer

In the 1970s, tamoxifen became widely accepted by oncologists for the management of metastatic breast cancer, not only because of its efficacy, but also because its toxicity was less than that of diethylstilbestrol (DES), the hormonal treatment previously preferred. In addition to its favorable toxicity profile, tamoxifen produced a high percentage of objective remissions. It seems that tamoxifen became the preferred treatment for the palliative management of metastatic breast cancer almost overnight, and DES has not been used in a long, long time.

During that time period, we learned the importance of stable disease with improved performance status. Patients with stable disease frequently felt better and were continued on tamoxifen. In addition, some patients who initially did not show an objective response to tamoxifen were continued on tamoxifen therapy and eventually did demonstrate an objective complete or partial response. This finding was significant for the role of hormonal therapy in the 1970s and beyond.

During the 1970s, it was thought that chemotherapy might provide a cure for metastatic breast cancer. After the subsequent disillusionment with chemotherapy as a curative modality set in, hormonal therapy returned to prominence for the palliation of hormone-responsive metastatic disease--essentially a chronic but still incurable condition. Tamoxifen has emerged as the standard of care for first-line treatment of metastatic disease in pre- and postmenopausal women with estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive breast cancer. With the rise in the adjuvant use of tamoxifen, many patients are already taking or have recently discontinued tamoxifen at the time of first metastasis. Thus, the use of tamoxifen monotherapy for metastatic disease is no longer as common.

Adjuvant Therapy

In considering adjuvant therapy for breast cancer, the major goal of treatment is to prolong survival while maintaining an acceptable quality of life. In addition to overall survival--the major end point--we must recognize that prolonged periods of disease-free survival are not only a harbinger of overall survival to come, but a worthy goal in its own right. When a breast cancer patient is free of...
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metastatic disease, her psychological as well as physical quality of life is much better than after
diagnosis of metastatic disease.
In the 1970s, some physicians refused to recognize the benefit of prolonged disease-free survival
and thus refused to treat these patients with adjuvant therapy. We cannot minimize the effect on an
individual patient of developing metastatic disease when she has been disease free for a long period
of time. And such effects may not be seen in meta-analyses and overall survival data. When a
patient who has been free of breast cancer for 10 years develops metastases, she becomes a
candidate for palliative treatment. This has an enormous effect on quality of life because the disease
becomes part of her everyday life. Thus, we believe that prolonged periods of disease free survival
are advantageous in their own right.
Our thinking on the adjuvant use of tamoxifen has evolved over the years as a result of increasing
experience and data from ongoing trials. In the 1985 National Cancer Institute (NCI) Consensus
Development Conference on Adjuvant Chemotherapy for Breast Cancer,[1] the question of how to
treat patients outside clinical trials arose. Most participants thought that every patient should be
enrolled in a trial; however, the actual percentage of eligible American patients entered into
adjuvant trials at that time was less than 3%. The turning point in the conference came when a
physician from rural Georgia stated that the lack of guidelines was not helpful to either patients or
doctors in the community. The Consensus Conference developed the 1985 guidelines to aid
physicians in selecting the most appropriate therapy for patients not entered into a trial (Table 1).
These were merely guidelines and were not rigid because physicians cannot treat cancer patients
simply by following general recommendations; there are always nuances in the care of an individual
patient.
As a result of this consensus conference, tamoxifen was established as the standard of care for
postmenopausal patients with positive axillary lymph nodes and positive hormone receptors. This
was a major step forward in opening the door for additional studies on adjuvant use of tamoxifen. At
that time, the recommendation for adjuvant chemotherapy in premenopausal, node- negative,
high-risk patients was controversial.
Following the publication of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis
of adjuvant trials,[2] a pivotal conference was held at St. Gallen in 1988 during which slightly
different guidelines and treatment criteria were developed (Table 2).[3] Chemotherapy was
recommended for node-positive, premenopausal patients with either positive or negative receptors.
Tamoxifen remained the standard of care for the node-positive postmenopausal, receptor-positive
patient, but chemotherapy was considered as an investigational option. For the first time,
chemotherapy for the receptor-negative postmenopausal patient gained some credibility,
particularly among the Europeans.
This was a significant change at that particular time. Chemotherapy for the high-risk, node-negative
patient was considered more as a proactive recommendation, and tamoxifen for the low-risk patient
was certainly promulgated. At the time of that conference in 1988, the arbitrary definitions of low vs
high risk were very similar to what they are today, except that the primary tumor size as a risk factor
is now greater than two cm, while other prognostic parameters remain very similar.

Unanswered Questions

It is interesting to consider what questions were unanswered in 1988 (Table 3) and if they remain
unanswered today, eight years later.
The appropriate duration of tamoxifen, especially in the node-positive patient, is still an open
question despite the availability of additional data in node-negative patients.
The appropriate timing of tamoxifen combined with chemotherapy, using it concurrently or
sequentially, has not been determined. In the United States, most oncologists give tamoxifen after
the completion of combination chemotherapy. However, there are data from the National Surgical
Adjuvant Breast Project (NSABP) on the benefit of the concurrent use of tamoxifen with
cyclophosphamide and doxorubicin.[2]
The role of ovarian ablation and/or tamoxifen in premenopausal, node-positive patients when
compared with chemotherapy alone has not been defined. EBCTCG data from 1995 suggest that
there is no additional advantage to ovarian ablation in the presence of chemotherapy. Additional
trials, including a large intergroup trial, will hopefully provide a definitive answer.
The role of tamoxifen combined with chemotherapy compared with tamoxifen alone in
postmenopausal, ER-positive, node-positive patients is an open question. In the United States, the
practice is most often to give chemotherapy followed by tamoxifen, while the practice in Europe has
generally been to give tamoxifen alone. Indirect evidence from the overview suggests chemotherapy plus tamoxifen may be more beneficial. A recent large intergroup trial in the United States should provide more data.

The role of tamoxifen plus chemotherapy compared with chemotherapy alone in postmenopausal, ER-negative, node-positive patients is still uncertain. In 1988, there was some feeling that these patients should also receive tamoxifen, but there is less support for this since the recent discussion of the 1995 overview results.

The role of tamoxifen in ER-negative, node-negative patients compared to chemotherapy alone is not yet defined.

**Second Consensus Conference**

A second NCI Consensus Conference was held in 1990 (Table 4).[2] One of the questions discussed was the role of adjuvant therapy for node-negative breast cancer. Although it was acknowledged that both tamoxifen and combination chemotherapy reduced the rate of recurrence, no treatment recommendations were given regarding the role of these two therapies. The only definitive statement from the 1990 conference is that patients with tumors one cm or less should not receive adjuvant therapy.

When the updated data from the Early Breast Cancer Trialists' Collaborative Group were published in 1992 (Table 5),[3] American oncologists were able to talk to the patients about the absolute benefits of treatment. This has led to more extensive discussions with patients about risks and benefits of treatment.

In 1992, another conference was held at St. Gallen. The guidelines generated at that time are shown in Table 6, Table 7, and Table 8. It was recommended that the minimal or low-risk, node-negative patient should receive either no additional systemic treatment or tamoxifen, and the good-risk patient should receive tamoxifen. The node-negative, high-risk, receptor-positive premenopausal patient should receive chemotherapy ± tamoxifen, a practice that has become more and more common in the United States. The node-negative, high-risk, receptor-negative premenopausal patient should receive chemotherapy alone. Of postmenopausal, node-negative, high-risk patients, those who are receptor positive should receive tamoxifen ± chemotherapy, whereas those who are receptor negative should receive chemotherapy ± tamoxifen. For the node-positive patient, the only real change was the recommendation for tamoxifen ± chemotherapy for the postmenopausal, receptor-positive patient.

The node-negative risk categories that most of us now accept were again refined at the 1995 St. Gallen Conference (Table 9). However, many oncologists in the United States also use flow cytometry results to aid in the selection of therapy for an individual patient. At the 1995 conference,[5] there were no changes in the recommendations for the minimal or low-risk node-negative patient (Table 10).

Although tamoxifen is considered investigational for the low-risk patient, some physicians are prescribing the drug because of its other benefits. Tamoxifen is the treatment of choice for the good-risk, node-negative, ER-positive patient of any age, with the use of ovarian ablation and chemotherapy being investigational. Chemotherapy ± tamoxifen is clearly the treatment of choice for the premenopausal, node-negative, high-risk patient. More and more women with ER-positive breast disease will be treated with tamoxifen and chemotherapy.

Tamoxifen is the treatment of choice for the postmenopausal, node-negative, ER-positive patient; however, more of these women will probably be receiving tamoxifen following chemotherapy, depending on the data from recently completed clinical trials.

**Duration of Tamoxifen**

The question of when to discontinue tamoxifen adjuvant therapy remains controversial. If one views patients with node-positive breast cancer, especially those with four or more positive nodes, as having a form of metastatic disease, it is a reasonable argument to continue tamoxifen beyond five years because the relapse rate over time is still great.

In our practice, we find that many node-positive patients want to continue tamoxifen because they feel that by taking it they are doing something proactive, and there is a life buoy effect. One concern these patients have relates to recurrence after stopping tamoxifen. In this case, will they blame themselves and their doctor? We still do not have definitive clinical trial data on the optimal duration of tamoxifen for node-positive patients.

In patients with node-negative breast cancer, there appears to be no benefit to prolonging tamoxifen...
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treatment beyond five years.[4]
The 1995 NCI Clinical Alert regarding tamoxifen duration has to be put into clinical context because results for node-positive and node-negative patients were not discussed separately. The document implies that tamoxifen should be stopped at five years for all patients. At the time the NCI Clinical Alert was issued, there were small numbers of node-negative patients at risk in the study. Although we understand why the Clinical Alert was issued, we do not take it to mean that the drug has to be stopped for node-positive patients. However, for node-negative patients, five years of tamoxifen is now the standard therapy.

We have heard some discussion that five years of tamoxifen is appropriate for node-negative patients, but we do not have good data on node-positive patients. Large clinical trials in estrogen receptor-positive, node-positive patients are required to further define the optimal duration of tamoxifen in this subset. At present we do not have the necessary data; we are extrapolating from the node-negative data.

Patient Communication

In the treatment of breast cancer, it is important to establish a relationship with the patient and ensure that the patient fairly and realistically understands the risks and benefits of any adjuvant treatment. Consensus conference statements and overview analyses are useful in the general sense, but the data have to be applied to the individual patient's needs. It is also important to ensure that the patient understands treatment benefits in terms of both relative and absolute benefits. Tamoxifen may decrease the risk of contralateral breast cancer from 2.0% to 1.3% at 10 years in absolute terms--a one-third reduction in relative terms. For some patients, a small absolute benefit may be an important factor in deciding treatment. The physician also has to mention other potential benefits of tamoxifen related to the cardiovascular system, bone mineral density, and lipids, especially if the patient has a history or risk in these areas. In addition, the physician also has to discuss the risks and put them into perspective for the individual patient.

Side Effect Profile of Tamoxifen

Tamoxifen is the most benign of all anticancer therapies we prescribe in terms of serious side effects. In our own practice, fewer than 1% of patients withdraw from adjuvant tamoxifen due to side effects. Weight gain and hot flashes are the most distressing symptoms to our patients. The weight gain is typically 3-15 lbs and occurs in about 30% to 40% of women on tamoxifen. The weight gain—not merely fluid retention—frequently cannot be avoided by diet and exercise and tends to remain after discontinuation of the drug. Weight gain can be particularly distressing to breast cancer patients because it affects body image, which is already adversely affected by breast cancer surgery, even if conservative surgical procedures are used.

Hot flashes clearly occur on tamoxifen and may be incapacitating in some cases. This symptom is sometimes alleviated by vitamin E, Bellergal spansules, clonidine, and other medications. Although vaginal dryness and a clear vaginal discharge are reported, they do not present a major problem for most women if vaginal lubricants are used. A small subset of women on the drug have reported emotional lability and memory loss, the latter of which reversed upon discontinuation of tamoxifen. We have not noted significant problems with nausea, skin rash, diarrhea, thrombocytopenia, leukopenia, thromboembolism, or liver function abnormalities.

Neither have we personally seen any cases of endometrial cancer among the several thousand patients treated. We warn patients about the slight increased risk of endometrial cancer. We stress the importance of routine gynecologic examinations and the importance of quickly calling to our attention vaginal bleeding so it can be investigated immediately. Very few patients will stop the drug because of fear of endometrial carcinoma. Patients understand that there is a risk of endometrial cancer, but do not appear to worry about it; they worry about their breast cancer.

Concern has been raised in the media about an association between tamoxifen and liver cancer based upon data in laboratory animals. We have not seen a single case of liver cancer among any of our patients treated. We have not seen any cases of endometrial cancer among the several thousand patients treated. We have not seen any cases of liver cancer among our own practice or in any published US study; several patients with alleged liver cancer clearly had metastatic breast cancer to the liver. Application of animal results to patients can be a problem, especially if there are extensive human data that contradict the animal data, as is the case with tamoxifen. Indeed, liver cancer is not included in our list of potential side effects.

Tamoxifen for the Prevention of Breast Cancer
There is no more important study that still needs to be completed than the National Surgical Adjuvant Breast Project (NSABP) Prevention Study. Due to some adverse publicity, crucial momentum was lost from this trial. There is a critical need for effective chemopreventive agents in light of genetic testing for cancer susceptibility genes. Today, the woman who carries the BRCA-1 and/or 2 genes has as her only options either increased surveillance, prophylactic mastectomy (leaving some breast tissue behind), or prophylactic oophorectomy. The risk/benefit profile for tamoxifen in this setting remains to be determined.

**Conclusion**

From a physician's point of view, tamoxifen is a remarkably effective drug. In the more than 20 years since tamoxifen was introduced in the United States, it has become the hormonal treatment of choice for breast cancer. For the breast cancer patient, the benefits of tamoxifen clearly outweigh the potential risks.

**References:**


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