More studies are needed to determine the optimal duration of tamoxifen treatment in patients with node-positive breast cancer.

Introduction

There are three reasons for the importance of understanding the appropriate duration of tamoxifen therapy.

First, defining optimum tamoxifen therapy duration would both maximize benefit and minimize toxicity. A substantial proportion of patients relapse in later years. ECOG trials show that 4.3% of patients recur annually between five and 10 years following diagnosis. Thus, clinical outcomes beyond five years after diagnosis remain an important question.

Second, economics are important. Tamoxifen is relatively expensive. In addition, side effects of any therapy, including tamoxifen, have expense. If we could minimize tamoxifen therapy duration, we also would minimize treatment expense.

Finally, there are fascinating biologic reasons to address this issue further. In essence, our understanding of the mechanism of action of tamoxifen and other hormonal agents is changing. Initial theories suggested these agents were cytostatic and essentially acted by "freezing" cells in the early G1 phase of the cell cycle. Thus, it was logical to hypothesize that it may be necessary to administer adjuvant tamoxifen indefinitely to keep the breast cancer cell frozen in the early G1 phase to prevent tumor regrowth. We know that tamoxifen also is cytotoxic for some breast cancer cells and capable of inducing apoptosis or programmed cell death. Thus, from a biologic standpoint, much of the impact of adjuvant tamoxifen therapy might be a short-term cytotoxic impact rather than simply a long-term cytostatic impact. This important biologic question warrants evaluation.

With these reasons in mind, investigators and co-operative groups have undertaken evaluation of the appropriate adjuvant tamoxifen therapy duration in both premenopausal and postmenopausal women with breast cancer. The current database regarding tamoxifen therapy duration remains limited but is rapidly growing. The Early Breast Cancer Trialists’ Collaborative Group performed a meta-analysis to compare the effects of less than and more than two years of adjuvant hormonal therapy with tamoxifen. This meta-analysis included data from 133 randomized trials involving 75,000 patients, 30,000 of whom were randomized to tamoxifen or no tamoxifen. The results certainly suggested a benefit for women receiving more than two years of tamoxifen therapy. For patients who receive one year or less of treatment, the benefit was less than that observed for patients receiving two or more years of tamoxifen (Table 1). This benefit appears particularly important for premenopausal women. Whereas one sees benefit with relatively short durations of adjuvant tamoxifen for postmenopausal women, the meta-analysis results suggest premenopausal women gain little or no benefit until they have received more than two years of adjuvant tamoxifen therapy.

Based on these results, I think we are all comfortable with recommending more than two years of adjuvant tamoxifen therapy. The current controversy now focuses on the appropriate duration of adjuvant tamoxifen therapy beyond two years. Four recent studies evaluated duration of tamoxifen therapy: two studies compared two vs five years of tamoxifen therapy, and two compared five vs more than five years of therapy.

The two studies comparing two vs five years of therapy clearly demonstrated a disease-free survival benefit for patients receiving tamoxifen for five years (Table 2).
The Swedish trial also demonstrated an overall survival benefit for those patients receiving five years of tamoxifen. Both trials comparing five vs more than five years of therapy included women who were axillary lymph-node-negative. The Scottish trial also did not exclude patients based on estrogen receptor status. Although both studies reported a small number of events over the follow-up period, there apparently was no benefit to continuing adjuvant hormonal therapy past five years.

Further, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial, there appeared to be a small, nonsignificant but provocative actual decrease in disease-free and overall survival for patients who received prolonged adjuvant tamoxifen therapy. In this trial, the disease-free and four-year overall survival in patients receiving five years of tamoxifen were 92% and 96%, respectively. In comparison, patients receiving more than five years of tamoxifen demonstrated a lower disease-free (86%; P=.003) and four-year overall survival (94%; P=.08), respectively.

These results suggest that adjuvant tamoxifen therapy for two to five years after primary treatment will decrease the annual odds of recurrence by approximately 30% and death by approximately 20% each year for at least 10 years. However, in the axillary lymph node-negative setting, we currently have no striking evidence to suggest a benefit for continuing adjuvant tamoxifen therapy beyond five years.

The lymph-node-positive group represents a somewhat different challenge and concern. Lymph-node-positive patients are at higher risk for eventual recurrence and death due to breast cancer, so one would expect a larger number of events in this group. Thus, in balancing risk and benefit with tamoxifen in these patients, the concern is that the higher risk of recurrence and relatively greater benefit of continuing tamoxifen might overshadow concerns over tamoxifen side effects. One trial evaluating tamoxifen therapy in this population was recently reported by ECOG. In two trials, patients received one year of adjuvant chemotherapy followed by four years of adjuvant tamoxifen and were then randomized to continued adjuvant hormonal therapy or observation. Both trials included estrogen receptor-positive and estrogen receptor-negative patients. Overall, there was no survival advantage for patients receiving prolonged tamoxifen compared with those stopping at five years after initial diagnosis. However, a small subset of patients who were estrogen receptor-positive and received continuous adjuvant tamoxifen had a lower relapse rate compared with estrogen receptor-positive patients who did not continue tamoxifen (P=.04). This difference was not accompanied by a difference in overall survival.

Each of these trials included relatively small numbers of patients and reported only a small number of events, which suggests a statistically significant benefit may not be achieved. A basic problem in this area is the ready assumption that we may be able to get a quick, cheap answer from one, two, or three trials. From our early experience with adjuvant tamoxifen therapy, we recognize that the benefit of adjuvant tamoxifen therapy is relatively modest, and we had to perform a meta-analysis on 33 trials to demonstrate it. We currently lack a database of that size to compare the benefits and risks in patients receiving 10 vs five years of adjuvant tamoxifen therapy. Thus, we do not yet have a complete or compelling answer, and we definitely need more data before we are certain that adjuvant hormonal therapy has no benefit beyond five years.

Other Ongoing Trials

**DR HORTOBAGYI**

There is a large international trial, the ATLAS trial, that will also address this issue using a very simple trial design to accrue several thousand patients. Several other trials also will address the issue of optimal tamoxifen therapy duration (Table 3). I was involved in the decision to close the NSABP B-14 trial. At the time of our decision, there was not only no improvement associated with adjuvant tamoxifen given for more than five years, but also a trend in the wrong direction. The statistical analysis of that trial and previous experience with untreated node-negative patients suggested that, despite the enrollment size, the expected number of events over five to 10 years would not demonstrate a difference between the groups without a major, very dramatic change in the natural history of the disease. Thus, the trial was closed because it could not possibly detect a benefit with the number of enrolled patients.

**DR REINTGEN**

Is the risk of contralateral disease a reason to continue tamoxifen beyond five years in patients with treated breast cancer?

**DR HORTOBAGYI**

Data suggest that tamoxifen decreases the contralateral breast cancer risk by 39%. However, the absolute contralateral breast cancer rate decreases from only 2% to 1.4%. Because women who develop contralateral disease are closely monitored, they are diagnosed in early stages with their second breast cancer, and the expected
Biologic Aspects of Long-term Tamoxifen

**DR HORTOBAGYI**

I would like to address the biologic perspective of the tamoxifen controversy. We all assume that therapy can have only beneficial effects. Several investigators have shown in vitro that longer exposure to tamoxifen in culture results in longer breast cancer cell-growth suppression.\(^{14-16}\) However, approximately 20% to 30% of these cells not only start growing despite tamoxifen but also change their biologic characteristics. These cells have adapted to the medium and are now dependent on the continued presence of tamoxifen for growth. If one were to extrapolate these findings to the clinical setting, one could also look at prolonged tamoxifen administration as precipitating and enhancing the recurrence rate in some patients. This phenomenon may have contributed to the dilution of some of these trial results. We may find that some patients may benefit from prolonged tamoxifen administration but others may be harmed. The challenge is not only to decide whether more than five years of tamoxifen is beneficial, but also to address whether we can identify biologic subgroups that may or may not benefit from prolonged tamoxifen treatment. Alternatively, it may be possible to develop monitoring systems for minimal residual disease that identify subgroups that may not benefit from continued tamoxifen administration.

**DR SLEDGE**

Dr Hortobagyi is absolutely right. I think the related question is whether tamoxifen is the best drug to use as adjuvant hormonal therapy. In the future, we will have true antiestrogens for adjuvant breast cancer therapy. Tamoxifen is not a pure antiestrogen; it has weak estrogen-agonist activity in some tissues.\(^{17}\) In metastatic breast cancer, there are some trials with relatively pure antiestrogens to which patients appear to respond after having failed on tamoxifen.\(^{18}\) We may be able to use these new agents in the adjuvant setting to attain equivalent or improved efficacy and avoid the problems Dr Hortobagyi has mentioned.

Nodal Status and Tamoxifen Therapy

**DR HORTON**

I think most would agree that five years is a reasonable treatment duration for tamoxifen for the node-negative population. However, I have many patients with involvement of five or more nodes who are taking tamoxifen and remain free of disease at five years. While recognizing that there may be some biologic harm, it is difficult to change the status quo and recommend stopping tamoxifen. Outside the context of a clinical trial, what do you currently recommend for patients with at least five positive nodes and positive hormone receptors who have been taking tamoxifen for five years or longer?

**DR SLEDGE**

I personally have managed these patients on a case-by-case basis and discussed the controversy with each patient. Patient preferences vary depending on perception of risk and the degree of toxicity experienced. The patient who has been chronically miserable and depressed and who has had night sweats from which she has awakened three times a night for the past three years may be more willing to discontinue tamoxifen than the patient with eight positive nodes who has had absolutely no side effects and is now disease-free five years after diagnosis. I think the decision to continue therapy should be made on a case-by-case basis.

**DR HORTOBAGYI**

I agree. I have discussed these issues with all of my patients. Some have elected to continue treatment and others have discontinued treatment. I do not have a general rule. However, I tell new patients for whom I initiate tamoxifen therapy that I will stop therapy at five years until better data become available.

Monitoring for Endometrial Cancer

**DR HORTON**

Do you have specific guidelines for monitoring women for endometrial cancer who receive long-term tamoxifen?

**DR SLEDGE**

The endometrial cancer question is continually vexing. The number of patients who develop endometrial cancer while on tamoxifen therapy is so small. I came to Indiana University in 1983 and have run the breast cancer clinic there since that time. Last week, I saw my third case of endometrial cancer in a patient receiving adjuvant tamoxifen. In general, a patient receiving tamoxifen may have a one in 1,000 excess annual risk of endometrial cancer. With that level of risk, there currently is no uterine screening procedure that would be cost effective. It is difficult to imagine that routine endometrial biopsy or transvaginal ultrasound will ever be cost effective to identify patients with endometrial carcinoma. Thus, I currently recommend annual Pap smears, pelvic examinations, and immediate report of any uterine symptomatology, which also are the recommendations of the American College of Obstetrics and Gynecology.

**DR HORTOBAGYI**

At M.D. Anderson, we advise patients to continue getting their usual annual gynecologic examinations. We do not routinely perform any other intervention or uterine monitoring such as annual ultrasound, transvaginal ultrasound, or endometrial biopsy. Importantly, however, we do educate patients who use tamoxifen regarding what symptoms and signs of concern should be reported.

References