Highlights from Recent National Surgical Adjuvant Breast and Bowel Project Studies in the Treatment and Prevention of Breast Cancer

Bernard Fisher, MD

Abstract
Findings from major National Surgical Adjuvant Breast and Bowel Project studies in women with breast cancer and negative axillary nodes are reported and discussed.
Results of the B-13 and B-19 studies demonstrated that systemic chemotherapy (either with methotrexate and sequentially administered fluorouracil followed by leucovorin, or with cyclophosphamide plus methotrexate and fluorouracil) increased overall disease-free survival in women 49 years of age or younger, as well as in those 50 years old or older. Women older than 50 also experienced a survival advantage with chemotherapy. Moreover, women who received systemic chemotherapy after lumpectomy plus radiation therapy were significantly less likely to develop an ipsilateral recurrence of tumor.
The B-14 study established the benefit of tamoxifen. When chemotherapy was added to tamoxifen in the B-20 trial, there was an increased benefit.
The B-18 trial demonstrated that the outcome of patients who received preoperative chemotherapy was comparable to that of patients who received the same therapy postoperatively. Moreover, results suggested that breast tumor response to preoperative chemotherapy correlated with outcome. Also, larger tumors were sufficiently downstaged by preoperative chemotherapy to permit lumpectomy rather than mastectomy.
The B-17 study in women with ductal carcinoma in situ concluded that radiation therapy should follow lumpectomy in women with localized, mammographically detected lesions.
The P-1 Breast Cancer Prevention trial showed that tamoxifen was effective in significantly reducing the incidence of both invasive and noninvasive breast tumors in women at high risk for the disease. Although many questions remain, and a new study, P-2, has been designed to compare tamoxifen and raloxifene, it is appropriate to offer tamoxifen to women who are similar to those in the P-1 study and who may benefit from it. (CA Cancer J Clin 1999;49:159-177.)

Introduction
April 4, 1998, the 40th anniversary of the National Surgical Adjuvant Breast and Bowel Project (NSABP), also marked...
the 40th anniversary of the enrollment of the first patient into a randomized clinical trial designed to determine the worth of systemic adjuvant chemotherapy for the treatment of operable breast cancer.

That trial was the first effort of 23 surgeons who were the founding members of the NSABP. At that time, none of us could have predicted either the longevity of that organization or the magnitude of the impact its work would have on the understanding and treatment of breast cancer during the four decades that followed. Moreover, we could not have anticipated that thousands of physicians, nurses, and support staff from hundreds of institutions would eventually participate in NSABP clinical trials, or that 50,000 women would voluntarily enroll in those studies, whose findings would ultimately be of benefit to future generations of breast cancer patients and to women at increased risk for the disease.

It is not possible in this brief report to present all of the findings from NSABP studies that have advanced local-regional and systemic therapy for stages I and II breast cancer during the past 40 years. Details of those studies describe how our efforts have played a seminal role in the evolution of systemic chemotherapy and hormonal therapy and have resulted in the replacement of radical breast cancer surgery with breast-conserving operations.1-8

In this report, we will discuss findings of NSABP studies conducted during the past decade that were designed to answer the following four questions: (1) What is the appropriate treatment for patients with early-stage—i.e., node-negative—breast cancer? (2) What is the role of preoperative chemotherapy? (3) How should intraductal carcinoma (ductal carcinoma in situ, DCIS) be managed? and (4) Is tamoxifen effective as a breast cancer preventive agent?

The issues that have arisen as a consequence of these study results and the ways in which these findings should be applied, both in breast cancer treatment and prevention, will also be considered.

**Systemic Therapy for Patients with Negative Axillary Nodes**

At a National Institutes of Health Consensus Conference held in 1985, it was concluded that a lack of information precluded recommending therapy other than surgery for breast cancer patients with negative axillary nodes.9 Findings from the following four NSABP randomized clinical trials involving more than 8,000 patients have subsequently indicated the propriety of using breast conservation, postoperative breast irradiation, and systemic therapy to treat these women.

**NSABP Studies: B-13 and B-19 (Estrogen-Receptor-Negative Tumors)**

Two major NSABP clinical trials, B-13 and B-19, were conducted to evaluate the worth of adjuvant chemotherapy in patients with estrogen-receptor (ER)-negative tumors.

**Design**

In B-13, 760 women were randomly assigned to receive either methotrexate (M) and sequentially administered fluorouracil (F) (M➔F) followed by leucovorin, or to surgery and no chemotherapy.10,11 In B-19, a total of 1,095 women with the same eligibility requirements were randomly assigned to receive either M➔F or cyclophosphamide (C) together with M➔F (CMF) as conventionally used.11

The aim of the B-19 trial was to determine if the alkylating agent cyclophosphamide contributed an additional benefit when used in a chemotherapeutic regimen. Data from both studies demonstrated the worth of the regimens being evaluated, yielded information about the natural history of patients with negative nodes, and set the stage for a new generation of NSABP trials designed to evaluate other ther-
apeutic regimens in such patients.

Findings

In the B-13 study, after eight years of follow-up, the overall disease-free survival of patients treated by surgery alone was only 59%, an indication that node-negative patients with ER-negative tumors did not have as favorable a prognosis as had previously been believed. Women in both younger (age 49 or younger) and older (age 50 and older) groups, however, experienced a significant increase in overall disease-free survival after therapy with $M\rightarrow F$ (74% at eight years; $p<0.001$). Moreover, a survival advantage was observed in the older group of patients (89% vs 80%; $p=0.03$).

Through five years of follow-up in the B-19 study, an overall disease-free survival advantage (82% vs 73%; $p<0.001$), as well as a borderline survival advantage (88% vs 85%; $p=0.06$), was observed for patients who received CMF. The benefit associated with CMF versus $M\rightarrow F$ was greater among women in the younger age group. Although a benefit from CMF was also observed in women 50 years of age or older, it approximated that from $M\rightarrow F$.

Of importance were the findings that indicated a low probability of ipsilateral breast tumor recurrence after treatment with lumpectomy and breast irradiation followed by chemotherapy. In the B-13 study, the frequency of ipsilateral breast tumor recurrence after treatment with lumpectomy and breast irradiation alone was extremely low in women who received $M\rightarrow F$ (2.6%) and CMF (0.6%), as compared with those who received no chemotherapy (13.4%).

Conclusions

Findings from both of these trials led us to conclude that $M\rightarrow F$ and CMF were effective for women with ER-negative tumors and negative axillary nodes. In the younger age group, treatment with CMF resulted in a clearly better disease-free survival and survival; in the older age group, a benefit from both regimens was apparent, although it was less clear which regimen was most effective. Because severe toxicity was less frequent after $M\rightarrow F$ therapy, that regimen was recommended for older women with associated medical problems that would preclude the use of more toxic agents.

The remarkably low incidence of ipsilateral breast tumor recurrence after either drug regimen plus breast irradiation after lumpectomy further justified the use of breast-conserving surgery for most women with breast cancer. Those findings support the author’s long-held contention that the effect of local-regional therapy, i.e., surgery and radiation, should no longer be considered independent of the effect of systemic therapy.

NSAP Studies: B-14 and B-20 (Estrogen-Receptor-Positive Tumors)

Two additional trials, B-14 and B-20, were conducted by the NSABP in patients with ER-positive tumors. The aim of B-14, a randomized, double-blind, placebo-controlled trial initiated in 1982, was to determine the effectiveness of adjuvant therapy with tamoxifen in patients with negative axillary nodes. That study, which involved more than 2,800 randomized and 1,200 registered tamoxifen-treated patients, has, arguably, provided some of the most compelling information gathered during the past decade.

Before the B-14 findings became available, however, we concluded that the degree of benefit achieved with tamoxifen in this patient population was unlikely to be sufficiently great to eliminate the need for other trials to test potentially more effective regimens.

As a result of that consideration, another NSABP trial (B-20) that involved more than 2,300 women was initiated to test the hypothesis that the addition of either $M\rightarrow F$ or CMF to tamoxifen (MFT, CMFT) would result in a greater benefit than that which could be achieved with
tamoxifen alone. Findings from both of these studies have dramatically altered our thinking regarding the management of this patient population. In addition, the B-14 findings have provided both biologic and clinical justification for studies related to breast cancer prevention.

**Findings**

Through 10 years of follow-up in the B-14 trial, a significant advantage was observed in disease-free survival (69% vs 57%, p<0.0001) and survival (80% vs 76%, p=0.02) among tamoxifen-treated women 49 years of age or younger and 50 years old or older. Tamoxifen therapy was also associated with a 37% reduction in the incidence of contralateral breast cancer (p=0.007). No additional benefit, however, was observed from tamoxifen administration beyond five years.

In the B-20 study, chemotherapy plus tamoxifen resulted in significantly better disease-free survival than that observed with tamoxifen alone (90% for MFT vs 85% for tamoxifen [p=0.01]; 89% for CMFT vs 85% for tamoxifen [p=0.001]). A similar survival benefit was observed (97% for MFT vs 94% for tamoxifen [p=0.05]; 96% for CMFT vs 94% for tamoxifen [p=0.03]).

When compared with tamoxifen alone, MFT and CMFT reduced both the rate of ipsilateral breast tumor recurrence after lumpectomy and the rate of recurrence at other local, regional, and distant sites. Of particular significance was the observation that the rate of treatment failure was reduced after the administration of both types of chemotherapy, regardless of the size of a patient’s tumor, degree of tumor ER positivity, progesterone-receptor level, or age. In addition, we failed to identify any subgroup of patients who did not benefit from chemotherapy.

**Conclusions**

Because the B-14 findings showed that tamoxifen significantly reduced the rate of treatment failure at local and distant sites, the rate of tumors in the contralateral breast, and the incidence of ipsilateral breast tumor recurrence, and because all subgroups of patients benefited and the benefits were attained with a relatively low incidence of undesirable side effects, we initially concluded that tamoxifen was justified for women who met the eligibility criteria of the study participants. However, because patients with small (1 cm or less), mammographically identified lesions were rarely enrolled in the B-14 study, no information was obtained to indicate whether or not such women should receive tamoxifen.

When analyses of the B-20 study failed to identify a subgroup of women with ER-positive tumors and negative nodes who failed to benefit from either MFT or CMFT, we concluded that all women similar to those in the trial might be considered candidates for chemotherapy plus tamoxifen. As in B-14, however, only a few patients with tumors of 1 cm or smaller had been entered into the B-20 trial. Consequently, we did not have sufficient information on which to base conclusions about whether such patients should receive chemotherapy.

**COMMENTARY: TREATMENT OF NODE-NEGATIVE PATIENTS**

The findings from the four studies conducted in axillary node-negative patients raised several issues. Figures 1 and 2 show that after surgery alone the overall prognosis of such patients is sufficiently poor to warrant the use of systemic therapy. In fact, the prognosis of some of these women may be worse than that of women with positive nodes. That situation prevails in women with ER-negative as well as in women with ER-positive tumors. Although these findings demonstrate a less-than-favorable prognosis for women with negative nodes, they do indicate that an appreciable number of them, regardless of the ER content of their tumors, could remain free of disease even if they did not receive systemic therapy.
Aside from the patients in the four studies who did not need systemic therapy, some women derived substantial benefits. In those with ER-negative tumors, there was about a 20% benefit in disease-free survival and about a 10% improvement in survival at eight years as a result of chemotherapy. When tamoxifen was given to women with ER-positive tumors, a 10% improvement in disease-free survival and about a 5% benefit in survival were observed.

The benefit increased when chemotherapy was given in addition to tamoxifen. There was about a 25% improvement in disease-free survival, and the small but significant survival benefit that resulted from tamoxifen was amplified when chemotherapy was also administered. The data in Figures 1 and 2 also show that, except for those women who either benefited from or who did not need adjuvant systemic therapy, approximately one fifth to one fourth failed to derive a benefit with respect to disease-free survival, and about 10% to 20% experienced no survival benefit.

**Identifying Patient Subgroups**

These results give rise to several impor-
tient questions: One relates to whether, at the time of diagnosis, subgroups of patients can be identified that either do not need or do not benefit from the therapies that have demonstrated an overall advantage. Statistical analyses conducted in search of inconsistencies in treatment effect among node-negative patients in our studies did not identify any subgroup of women with either ER-negative or ER-positive tumors who did not benefit from systemic adjuvant therapy—i.e., chemotherapy in the former and tamoxifen plus chemotherapy in the latter.

As previously mentioned, because none of our studies enrolled enough women with occult, mammographically detected invasive tumors of 1.0 cm or less in size, and because sufficient events have not yet been observed in those who have entered the studies, definitive information about the propriety of using tamoxifen and/or chemotherapy for the management of such patients is not available.

Consequently, when asked the question, Should all patients with negative nodes and ER-positive tumors be treated with tamoxifen plus chemotherapy? we

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**Figure 2**

Magnitude of Disease-Free Survival and Survival (Node-Negative, ER-Positive Tumors)

Benefits achieved with tamoxifen alone or with tamoxifen plus adjuvant chemotherapy in axillary node-negative patients with ER-positive tumors.
are unable to provide as precise an answer as we would like, despite the extent and credibility of our findings. Certainly, there are patients who either will not benefit from or will not need such therapy. Unfortunately, we have been unable to identify these women with precision.

Consequently, we have taken the position that, until markers are found that can identify these women with greater certainty than now exists, patients should not be denied the chance to either accept or reject the opportunity to receive the benefit that has been demonstrated. There will, of course, always be mitigating circumstances that prevent administration of a particular therapy to certain patients. That dilemma, in turn, gives rise to a series of questions such as, Is the benefit demonstrated by the therapy adequate to justify the treatment? How is the benefit balanced against the toxicity, the cost of the treatment, and other variables? As has previously been pointed out, because there are no criteria for answering these questions, therapeutic decision making often remains a value judgment.

**Heterogeneity of Outcomes**

Recently, in an attempt to identify subpopulations of node-negative women with ER-positive tumors who require more aggressive forms of therapy and to distinguish them from women for whom such therapy is unnecessary, we assessed the outcome, through 10 years of follow up, of more than 4,000 node-negative patients in B-14 who received either placebo or tamoxifen, taking into account their age at surgery, ER status, progesterone-receptor status, tumor size, tumor S-phase fraction, and tumor nuclear grade. Tumor size and S-phase were viewed as continuous variables.

Perhaps the most significant of our findings was the observation of an extreme heterogeneity of outcomes among a population that has, until recently, been considered to have a favorable prognosis. For example, the 10-year disease-free survival for 35-year-old women in the B-14 trial varied from about 80% to less than 40%, depending upon the interaction of the various prognostic variables being assessed (Fig. 3).

Thus, a group of node-negative patients who received tamoxifen or placebo consisted of women who displayed myriad heterogeneous outcomes. These observations indicate that more aggressive therapy is warranted for some but not all patients in the node-negative, ER-positive population. The appropriate selection of therapy requires an accurate assessment of each individual patient’s prognosis.

**The Role of Preoperative Chemotherapy in the Treatment of Breast Cancer**

Hypotheses formulated on the basis of biologic and clinical information obtained during the 1980s led to the initiation of an NSABP trial (B-18) to evaluate the worth of preoperative (also known as neoadjuvant, primary, or induction) chemotherapy for the treatment of primary operable breast cancer. The chief aim of that study was to determine whether such therapy could more effectively prolong disease-free survival and survival than did the same therapy administered postoperatively.

A second objective was to evaluate the response of a primary tumor to preoperative chemotherapy and to correlate that response with disease-free survival, recurrence-free survival, and overall survival rates. If a correlation could be demonstrated, it was thought that breast tumor response could serve as an indicator of the response of micrometastases to the therapy.

Moreover, it was also believed that it might be possible to use local tumor response to determine whether or not more of the same therapy—or another type of systemic therapy—should be administered. A third aim was to determine whether the use of preoperative chemotherapy would permit more lumpectomies to be performed in pa-
patients considered to be candidates for mastectomy, and, in that regard, to decrease the incidence of ipsilateral breast tumor recurrence after such surgery. An additional objective was to ascertain whether preoperative chemotherapy increased the percentage of patients with negative nodes—i.e., downstaged their axillary lymph-node status.

NSABP STUDY: B-18

In the B-18 trial, more than 1,500 women were randomly assigned to one of two treatment groups. Women in group 1 received doxorubicin (Adriamycin, A) and cyclophosphamide (Cytoxan, C) [AC] therapy every three weeks for four cycles, postoperatively; those in group 2 received the same therapy preoperatively. Women 50 years of age or older also received tamoxifen.

Findings

An initial report from B-18 described the effect of preoperative chemotherapy on local-regional disease. A complete clinical response of the primary breast tumor occurred in 36% of 683 patients; in 13% of all patients (36% of those with a complete clinical response), there was no evidence of invasive tumor on pathologic examination, i.e., there was a pathologic complete response. An additional 43% of patients treated with preoperative chemotherapy demonstrated a partial clinical response of greater than 50% of their breast tumors; in 17%, tumors remained clinically stable. Tumors continued to grow in only 3%.

The incidence of pathologically positive axillary nodes decreased from 57% in patients who received postoperative therapy to 41% in those treated with preoperative chemotherapy. More lumpectomies were performed, particularly in women whose tumors were 5 cm in size or larger and who had been candidates for mastectomy before treatment with preoperative chemotherapy.

When the effect of preoperative chemotherapy on the outcome of patients was evaluated, no significant differences

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TABLE 3

| Disease-Free Survival | Tumor size (cm) | S-Phase (%) |
|-----------------------|----------------|-------------|
| Progesterone Receptor-Positive | 1 | 2 | 3 | 4 | 5 |
| Progesterone Receptor-Negative | | | | | |

Outcomes among 35-year-old women with ER-positive tumors and negative axillary nodes; plotted as a function of S-phase fraction, clinical tumor size, and progesterone-receptor status.
in disease-free survival, distant disease-free survival, or survival were observed among patients in either group. Most important was the finding that the outcome of women whose tumors showed a pathologic complete response was better than that of those in whom invasive tumor cells were found on pathologic examination or in those whose tumors displayed a partial clinical response or who were clinical nonresponders. Findings relative to relapse-free survival rates through five years of follow-up were 86%, 77%, 68%, and 64%, respectively; p<0.0001) (Fig. 4).

Conclusions

Overall, preoperative chemotherapy was as effective as, but not more effective than, postoperative chemotherapy. Breast tumor response to preoperative chemotherapy correlated with outcome. Women whose tumors displayed a pathologic complete response had the greatest relapse-free survival and distant disease-free survival. Patients treated with preoperative chemotherapy underwent lumpectomy and radiation therapy more frequently, and the rates of ipsilateral breast tumor recurrence were similar in both treatment groups, particularly in patients who had large tumors and for whom mastectomy had been recommended.

Commentary: The Role of Preoperative Chemotherapy

Although preoperative chemotherapy failed to improve the overall benefit from chemotherapy beyond that achieved with postoperative therapy, the B-18 findings demonstrated that preoperative chemotherapy could be used in additional studies without decreasing disease-free survival and survival.

Of all the findings obtained in that study, most intriguing were those which demonstrated that the response of a primary breast tumor to preoperative chemotherapy related to subsequent patient outcome and that women with tumors that displayed a pathologic complete response to preoperative chemotherapy had a more favorable outcome than did those who experienced either a complete or partial clinical response.

Those findings showed that the response of a breast tumor to preoperative chemotherapy could serve as a surrogate or intermediate end point for determining the response of micrometastases to systemic therapy and, consequently, to distant disease-free survival and survival. Because breast tumor response can be determined within weeks after the administration of preoperative chemotherapy, it then becomes possible to predict a patient’s outcome and to provide her with that information so that she and her physician can consider other treatment strategies before a treatment failure occurs.

As a result of our findings with preoperative chemotherapy, we may now begin to evaluate, in that setting, new chemotherapeutic regimens alone, in combination, or in sequence with those that have already proven to be effective. Conclusions regarding their value can be drawn on the basis of their impact on the intermediate end point—i.e., breast tumor response. In addition, many prognostic tumor markers can now be evaluated in the preoperative setting with respect to how they correlate individually, or in combination, with tumor response and outcome, without a five- to 10-year wait for follow-up data, as has been the case.

Furthermore, it is now appropriate to evaluate the worth of promising new therapies such as anti-angiogenesis factors, growth-factor inhibitors, and anti-hormonal agents in the preoperative setting rather than in patients with advanced disease, because, in the latter, both the clinical and biologic status have been so altered as to make it unlikely that these agents will demonstrate any effect.

Finally, of particular clinical significance is the finding from B-18 demonstrating that the downstaging of large tumors after the use of preoperative
Highlights from NSABP studies

Chemotherapy permits more patients to be treated with lumpectomies. As a result of these observations, we have recommended that women whose tumors are judged by surgeons to be too large for lumpectomies, or whose surgeons are ambivalent about that procedure, initially have the option of receiving preoperative systemic therapy followed by lumpectomy and breast irradiation rather than mastectomy. It should be emphasized, of course, that there will always be patients whose lack of tumor response to such therapy will preclude breast-conserving surgery.

Treatment of Intraductal Breast Cancer

NSABP Study: B-17

Uncertainty regarding appropriate treatment for small, localized DCIS detected by mammography prompted initiation of...
the NSABP B-17 trial in 1985. The aim of that study was to test the hypothesis that excision of DCIS with tumor-free specimen margins (a procedure referred to as a lumpectomy, although most women did not have a palpable mass) followed by radiation therapy was more effective than lumpectomy alone in preventing the occurrence of a second tumor in the ipsilateral breast.

In 1993, we reported findings obtained from 818 randomized patients that showed, over five years of follow-up, that the event-free survival was significantly better for women who received radiation therapy after lumpectomy than for those treated by lumpectomy alone. A recent report of findings based on eight years of follow-up (mean follow-up time, 90 months; range 67 to 130 months) has confirmed our original conclusion and provided the basis for rational consideration of appropriate treatment for DCIS.

Findings

At eight years of follow-up, despite the requirement that the margins of resected specimens be tumor-free, the cumulative incidence of an ipsilateral breast tumor of any type that occurred in women whose DCIS was treated by lumpectomy alone was 27%, whereas, in women treated by lumpectomy followed by radiation therapy, it was 12% (Fig. 5). Although the cumulative incidence of noninvasive ipsilateral breast tumors was reduced from 13% to 8% in the two groups, respectively (p=0.007), of most significance was the reduction in invasive ipsilateral breast tumors, from 13% in the former group to 4% in the latter (p<0.0001). Particularly striking in that regard was our observation that the cumulative incidence of an invasive ipsilateral breast tumor remained virtually unchanged beyond the fifth year of follow-up.

The incidence of local-regional and distant events remained similar in both treatment groups, and deaths were only infrequently related to breast cancer. The overall survival of both groups was virtually identical (p=0.84). All subgroups of women benefited regardless of clinical or mammographic tumor characteristics. When the outcome of patients was examined relative to an array of pathologic and mammographic characteristics, we failed to identify a discriminant that identified DCIS patients who did not require post-operative radiation therapy.

Of particular interest were the findings obtained when prognostic variables were examined by multivariate analysis. When comedonecrosis and tumor margin status were examined together, women with tumor-free specimen margins and slight comedonecrosis had less chance of developing an ipsilateral breast tumor than did women considered to be at increased risk, i.e., those whose margins were not free of tumor and demonstrated moderate-to-marked comedonecrosis. However, not only did both categories of patients benefit from radiation therapy, but their outcomes also became similar after such treatment.

Conclusions

Radiation therapy should follow lumpectomy in women with localized, mammographically detected DCIS. No data are currently available to identify a subgroup of women with the kind of DCIS observed in this study who did not need to be treated with radiation therapy. Unfortunately, there are, as yet, no pathologic, mammographic, or biologic discriminants to indicate which patients either do not need, or will fail to benefit from, such therapy.

COMMENTARY: TREATMENT OF DCIS

The need for radiation therapy after lumpectomy in patients with DCIS continues to be a subject of controversy. Although there is agreement about the need to seek discriminants to identify patients who should receive breast irradiation, none have been identified. Consequently, we are, once again, faced with a dilemma. As we have already pointed out with
regard to the use of systemic therapy for node-negative patients, it would seem that the use of radiation therapy for all patients with the type of DCIS encountered in the B-17 study is appropriate. All women who can benefit from such therapy should have the opportunity to do so. That recommendation, however, does not imply that there are not certain patients for whom radiation therapy could be omitted. Rather, it indicates that there are currently no data available to identify with certainty which women should and which should not be so treated.

One attempt to devise such a scheme has resulted in the formulation of the Van Nuys Prognostic Index, a nomogram in which histologic type of DCIS, width of surgical excision margin, and tumor size were incorporated into a scoring schema.
purported to identify patients who should be treated by local excision alone, by local excision and radiation therapy, or by mastectomy. At present, the Van Nuys Prognostic Index has not been sufficiently validated; in addition, the index has shortcomings that preclude its use as part of a strategy for the treatment of DCIS. Moreover, because it was developed on the basis of data from patients with all sizes of DCIS, including tumors of 4.1 cm or more, the Van Nuys Prognostic Index is not applicable to DCIS patients in the B-17 study.

Some physicians still consider mastectomy the appropriate treatment for women with DCIS, even for the type of disease demonstrated by women in the B-17 trial. For a variety of reasons, we believe that there is no reasonable justification for treating small, localized DCIS with mastectomy.

Unpublished findings from a second NSABP randomized trial (B-24), which was conducted to evaluate treatment in patients with more extensive DCIS than that included in B-17, have shown that a woman’s risk of developing a subsequent invasive breast cancer in the ipsilateral breast was decreased when tamoxifen was given in conjunction with surgery and radiation therapy. Those findings should further diminish the justification for performing mastectomy to treat DCIS.

**Tamoxifen For Breast Cancer Prevention**

It was not until the mid-1980s that serious attention was given to chemoprevention, an approach aimed at reducing cancer risk by the administration of natural or synthetic compounds to prevent, reverse, or suppress carcinogenesis in individuals at increased risk for the disease. Tamoxifen was considered worthy of evaluation as a breast cancer preventive agent because it had been proven to be of value in treating advanced breast cancer, reducing tumor recurrence, and prolonging survival when administered as postoperative adjuvant therapy in stages I and II disease. Tamoxifen significantly reduced the incidence of contralateral breast cancer, interfered with the initiation and promotion of tumors in experimental systems, and inhibited the growth of malignant cells by a variety of mechanisms. Of major importance was the fact that most patients used tamoxifen safely and with good compliance and experienced relatively few side effects.

**NSABP Study: P-1**

Consequently, on June 1, 1992, the NSABP implemented the prevention trial (P-1), the primary aim of which was to determine whether tamoxifen administered for at least five years prevented invasive cancer in women at increased risk for the disease. Secondary aims were to determine whether tamoxifen lowered the incidence of fatal and nonfatal myocardial infarctions and reduced the incidence of bone fractures related to osteoporosis. Additional objectives were to evaluate breast cancer mortality and adverse effects from tamoxifen, as well as to obtain information about breast cancer genetics.

In the P-1 study, 13,388 women at increased risk for breast cancer were randomly assigned to receive either placebo or tamoxifen (20 mg/day) for five years. Women were considered to be at increased risk if they were 60 years of age or older, were between 35 and 59 years of age and had a five-year predicted risk for breast cancer of at least 1.66%, or had a history of lobular carcinoma in situ (LCIS). An algorithm based on a multivariate logistic regression model employing combinations of risk factors was used to estimate the probability (risk) of the occurrence of breast cancer over time. The variables included in the model were a woman’s age, number of first-degree relatives with breast cancer, nulliparity or age at first live birth, number of breast biopsies, pathologic diagnosis of atypical hyperplasia, and age at menarche.
Findings

Tamoxifen reduced the risk of invasive breast cancer by 49% (p<0.00001). The cumulative incidence of an invasive cancer through 69 months of follow-up was 43 versus 22 per 1,000 women in the placebo and tamoxifen groups, respectively. The decreased risk occurred in all age groups, and was 44% in women 49 years of age or younger, 51% in those between 50 and 59 years of age, and 55% in those 60 years of age or older. In women with a history of either LCIS or atypical hyperplasia, the risk of invasive cancer was reduced by 56% and 86%, respectively. The risk was also reduced in women with any category of predicted five-year risk. Tamoxifen reduced the risk of noninvasive breast cancer by 50% (p<0.002). Particularly important was the finding that the drug reduced the occurrence of ER-positive tumors by 69%, whereas there was no such reduction in the occurrence of ER-negative tumors. Although tamoxifen administration failed to alter the average annual rate of ischemic heart disease, it did result in a reduction in hip, radius (Colles’), and spine fractures.

An increased rate of endometrial cancer, predominantly in women 50 years of age or older, was observed in the tamoxifen group. All of the endometrial cancers that occurred in that group were stage 1 (localized disease), and no deaths from endometrial cancer were observed. No liver cancers or increase in colon, rectal, ovarian, or other tumors occurred in the tamoxifen group. However, higher rates of stroke, pulmonary embolism, and deep-vein thrombosis were observed more frequently in women 50 years of age or older who received tamoxifen.

Conclusion

After all aspects of this study were meticulously considered, it was concluded that, despite the side effects observed with tamoxifen, the drug sufficiently decreased the incidence of invasive and noninvasive breast cancer to warrant its administration in many women at increased risk for the disease.

COMMENTARY: FINDINGS FROM THE NSABP PREVENTION TRIAL

The P-1 study findings clearly demonstrate that tamoxifen reduces the risk of breast cancer in a substantial number of women at increased risk for the disease. As is evident, however, after each demonstration of a therapeutic advance, uncertainty arises with regard to the clinical application of the findings. Failure to resolve all of the issues and to answer all of the questions that have arisen as a result of the P-1 study does not necessarily detract from either the credibility or the importance of the findings, which have opened doors to new pathways for scientific investigation. In the following commentary, some of the concerns that have arisen subsequent to the publication of the P-1 findings will be addressed. More detailed information is presented in the report of the study findings.

Our use of the term prevention to describe the P-1 findings has engendered a great deal of controversy. When the study was designed, the term was used to indicate a reduction in the incidence (risk) of invasive breast cancer that occurred over the period of the trial. Whether the benefit was due to tamoxifen’s interference with the initiation and promotion of tumors or to the hindrance of the growth of occult tumors is unknown. Nonetheless, the absence of specific information to resolve the issue does not detract from the evidence that, in the P-1 trial, tamoxifen prevented the clinical expression of both invasive and noninvasive breast tumors—the goal of primary disease prevention.

Duration and Timing of Tamoxifen Administration

Some have expressed concern about the duration of tamoxifen administration. It has been speculated that, if the drug is given for only five years, tumor growth might...
merely be delayed for a short time and that, if tamoxifen fails to affect the process of tumor initiation and promotion, tumors will subsequently appear. Findings from NSABP B-14, however, which have been discussed earlier in this report, fail to support that concern. In that study, the benefit from five years of tamoxifen administration persisted through 10 years of follow-up. Giving the drug for more than five years failed to enhance its effect. Most important, the reduction in the incidence of contralateral breast cancer observed with five years of tamoxifen therapy continued through 10 years of follow-up; there was a 37% decrease at that time. Because the results from P-1, as those from B-14, demonstrated that the breast tumors prevented were ER-positive, it is likely that the benefit noted in the P-1 trial will persist after study participants discontinue taking tamoxifen. Although additional studies are necessary before the issue regarding duration of tamoxifen administration can be resolved, the value of five years of tamoxifen therapy cannot be disputed at this time.

Another important question concerns the optimal time to begin tamoxifen administration. It is likely that alterations were already present in the breast cells of women who developed tumors while on the P-1 study. Because their tumors were diagnosed early in the follow-up period, there would seem to be no merit in delaying administration of the drug to those women for whom it has been deemed appropriate.

**Adverse Events**

Both before and during the P-1 study, there was considerable concern with regard to reports about the dangers of liver damage, hepatoma, colon cancer, and retinal toxicity that might be associated with tamoxifen. Such events, however, have not been observed.

Even greater concern was expressed about the risk of endometrial cancer and vascular-related toxic effects, predominantly in postmenopausal women. The issue has been raised—primarily in the lay press—about whether the benefit from tamoxifen achieved by reducing the incidence of breast cancer was sufficiently great to justify its use as a chemopreventive agent despite the risk of those undesirable effects. Figures 6 and 7 represent a concise summary of the benefits achieved with tamoxifen and the risk of endometrial cancer and vascular-related events that appeared in the published report of the P-1 study.

In these Figures, each dot represents a single individual among 1,000 participants enrolled in P-1 who developed either an invasive or noninvasive breast cancer, an endometrial cancer, a pulmonary embolus, a stroke, or a deep-vein thrombosis over a five-year period—i.e., the rate per 1,000 women per five years. It is apparent that the number of symbols representing the rate of invasive and noninvasive cancers in the women who received tamoxifen was reduced by about one half; this indicates that the rates of cancer were reduced by half (Fig. 6).

The rate of endometrial cancer per 1,000 participants over five years in the placebo group was about five, and, in the tamoxifen group, about 12. Thus, there was, indeed, an increase in the rate of endometrial cancer in the tamoxifen group.

How may this increase be explained to a woman considering taking tamoxifen because she is at increased risk for breast cancer? Because women are at risk for endometrial cancer even if they do not take tamoxifen, to determine the rate of endometrial cancer due to tamoxifen, the rate in the placebo group should be subtracted from the rate in the tamoxifen group. Figure 7 shows that the overall rate of endometrial cancer resulting from tamoxifen administration is 0.7 per 100 women, or 0.7% over five years. A similar diagram of the undesirable vascular-related events that occur in women who take tamoxifen shows that, over a five-year period, the overall rate of stroke is between...
two and three per 1,000 women, or about 0.2% to 0.3% over five years. The rate of a pulmonary embolism is also about 0.2% over five years, and the rate of deep-vein thrombosis is between 0.2% and 0.3%. The rates of all of those events are lower for women 49 years of age or younger and somewhat higher for those who are 50 years of age or older. In the latter group, the rate of endometrial cancer is about 1% over five years whereas, for each of the vascular-related events, the excess rate is between 0.3% and 0.5%.

**Risk-Benefit Evaluation**

In view of the impressive benefits conferred by tamoxifen—i.e., the reduction in the risk of breast cancer (Fig. 6) and the relatively low rates of adverse events (Fig. 7)—it is reasonable to examine how such information should be used when the benefits and risks of using the drug for breast cancer prevention are being considered. Unfortunately, the attempt to assess quantitatively the magnitude of the benefit achieved—i.e., cancers prevented, versus the magnitude of adverse events that could occur, by subtracting the latter from the former—may not be appropriate because these are not of equal value.

To consider them to be so would be to suggest that, in the P-1 study, one disease was being “traded” for another. Using the occurrence of endometrial cancer as an example of an adverse event, it may be shown that such is not the case, for, if such an event should occur in a woman taking tamoxifen, it would likely be curable by hysterectomy, and the morbidity and mortality would be minimal. On the other hand, a breast cancer that might arise in a woman who had not received tamoxifen is more likely to be associated with greater morbidity and mortality as a consequence of the need for surgery, radiation, and systemic therapy.

If a net benefit cannot be achieved quantitatively, other issues must be considered by the physician as part of any risk-benefit evaluation. The woman for whom tamoxifen is being considered must be viewed as more than an individual at increased risk for breast cancer. Her physical well-being must be assessed to ensure that she does not have comorbid conditions that make the administration of tamoxifen not only undesirable but inappropriate. It is prudent to advise all women who receive tamoxifen to undergo an annual gynecologic examination and to report any abnormality that might be diagnosed. No information currently exists, however, to indicate that regular endometrial biopsies or examination by vaginal ultrasound should be necessary components of a gynecologic evaluation in women who receive tamoxifen.

**Candidates for Tamoxifen**

Who should consider taking tamoxifen to decrease the risk of developing breast cancer? Women younger than 50 years of age who meet the eligibility requirements of the trial are likely to be considered highly eligible for tamoxifen because their risk of an adverse event is practically nil, and the reduction in the incidence of breast cancer for the group overall is reduced by almost one half. Moreover, the greater the risk, the greater the benefit.

Postmenopausal women who have had a hysterectomy are also favorable candidates for tamoxifen because they cannot develop endometrial cancer. Because women with a history of LCIS or atypical hyperplasia are at particularly high risk for breast cancer, and because tamoxifen reduces that risk, the level of benefit achieved markedly outweighs the adverse effects that might result from the drug.

Also, because the risk of invasive breast cancer in women with localized DCIS is at least as high if not higher than that for women with a history of LCIS or atypical hyperplasia, the benefit they would receive from tamoxifen, insofar as reducing their rate of invasive breast cancer is concerned, is likely to eclipse the consequences of any adverse drug effects.
Consequently, they, too, may be viewed as candidates for the drug. Although, to date, no information is available to indicate whether women who are at increased risk for breast cancer because they carry BRCA1 or BRCA2 mutations should be considered candidates for tamoxifen, they should be afforded that option, particularly if they are contemplating having bilateral mastectomy to prevent breast cancer.

The decision to prescribe tamoxifen for women 50 years of age or older who have stopped menstruating, have not had a hysterectomy, and have no history of LCIS, DCIS, or atypical hyperplasia, is less clear. Because the incidence of adverse events remains constant regardless of the cancer risk in such women, it is evident that the greater the risk, the less controversial the issue. The greater the likelihood of mortality and morbidity associated with a breast cancer that might have been prevented by tamoxifen, the greater the benefit when balanced against potential adverse events. A precise level of risk, above and below which such a woman should or should not be considered a candidate for tamoxifen has not yet been determined and is likely to be difficult to agree upon.

Before the publication of the P-1 findings, the results from an English and an Italian trial, both of which failed to confirm our findings, were reported.26,27 None of the information presented in those studies alters our conclusion that tamoxifen significantly reduces the probability of breast cancer in women at increased risk for the disease. The P-1 study and the European trials were too dissimilar in design, population, and numerous other aspects to allow for valid comparisons among them. The relatively small number of participants, few breast cancer events, differing eligibility criteria, greater rates of noncompliance, and use of hormone replacement therapy associated with the European studies might account for the different results among the three trials.

**FUTURE PREVENTION STUDIES**

Although additional studies are needed...
to address the issues that have arisen as a result of the P-1 findings, on the basis of the data from that trial, we consider it highly appropriate to offer tamoxifen to women similar to those who participated in our study and who may benefit from its use as a breast cancer preventive agent. To that end, a new NSABP chemoprevention trial, P-2, will evaluate postmenopausal women who are at increased risk for breast cancer and are similar to those enrolled in P-1.

In P-2, the toxicity, risks, and benefits of the selective estrogen-receptor modulator raloxifene will be compared with those of tamoxifen. Although raloxifene has been shown to prevent osteoporosis, its value in reducing the rate of breast cancer without increasing the risk of endometrial cancer has not been established.

It must be emphasized, however, that the task of recommending tamoxifen for women at increased risk for breast cancer should be undertaken by only those primary health care providers who are free of personal bias, are knowledgeable about breast disease, know how to determine a woman’s risk for breast cancer and how to discuss with and counsel her about her individual course of action, and possess only complete and accurate information on the subject.

Breast Cancer: The Paradox of Accomplishment

This report has presented highlights of findings obtained during the past 10 years from NSABP randomized clinical trials. A comparison between the current findings and those reported in CA28 about a decade ago underscores the progress that has been made relative to the management of breast cancer patients. It also reveals, however, the lack of progress in resolving issues that continue to exist, the most important of which is the paradox that arises when each new report of an advance in breast cancer management results in a greater number of questions and more confusion about how individual patients should be treated.

Uncertainties about how to treat node-negative patients, particularly when their tumors are small; how to treat DCIS; who should receive preoperative systemic therapy; and who should be given tamoxifen to prevent breast cancer have all arisen as a result of the medical advances described in this report. However, it cannot be too strongly emphasized that, despite these still unresolved issues, thousands of women stand to benefit from the use of therapies that have evolved as a result of the findings from the NSABP studies described in this report.
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