

Physician Recommendations Regarding Tamoxifen and Patient Utilization of Tamoxifen after Surgery for Ductal Carcinoma in Situ

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BACKGROUND. To date, the impact of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial reported in 1999 on the use of tamoxifen after surgery for ductal carcinoma in situ (DCIS) is unknown. The current study was designed to evaluate the impact of NSABP B-24 on current practices at a comprehensive cancer center.

METHODS. The records of 350 consecutive patients with DCIS who were treated at the authors' institution between July 1999 and June 2002 were obtained from a prospective database and analyzed. Whether patients were offered tamoxifen, whether patients accepted tamoxifen, and the associated reasons were recorded along with tamoxifen-related side effects and patient compliance with therapy. Clinical and pathologic factors were evaluated for their impact on recommendations regarding tamoxifen. Differences were assessed by chi-square analysis.

RESULTS. Of the 350 patients, 73 were excluded because of evidence of invasive carcinoma on final pathology review. Of the remaining 277 patients, 166 patients (60%) were offered tamoxifen, and 90 patients (54%) chose to take tamoxifen. Of 111 patients who were not offered tamoxifen, 39 patients (35%) had documented explanations, which included bilateral mastectomy ($n = 25$ patients), medical reasons ($n = 10$ patients), and already received tamoxifen for other reasons at the time of diagnosis ($n = 4$ patients). Of 94 patients who received tamoxifen, 20 patients (21%) discontinued use because of side effects or complications. Tamoxifen was more likely to be recommended for women who underwent segmental resection compared with women who underwent total mastectomy ($P = 0.002$) and for women with smaller pathologic DCIS tumors ($P = 0.001$). In addition, these two factors were interrelated.

CONCLUSIONS. Physicians and patients remain cautious regarding the use of tamoxifen after local treatment for DCIS. The current findings have implications for current trials evaluating aromatase inhibitors and other chemopreventive agents for this disease. *Cancer* 2004;100:942-9. © 2004 American Cancer Society.

KEYWORDS: ductal carcinoma in situ (DCIS), tamoxifen, breast conservation, surgery.

The incidence of ductal carcinoma in situ (DCIS) continues to rise as breast carcinoma screening and awareness increase and as the techniques and interpretation of mammography continue to improve. DCIS currently accounts for approximately 20% of all screening-detected breast malignancies.¹ In 2003 in the U.S. alone, it was expected that > 47,000 cases of DCIS would be diagnosed.² Because both mastectomy and breast-conserving surgery with or without radiation therapy are effective surgical treatments for DCIS, treatment is chosen on the basis of patients' wishes and clinicopathologic factors. However, compared with mastectomy, breast-conserving surgery

TABLE 1
National Surgical Adjuvant Breast and Bowel Project B-24: 7-Year Cumulative Incidence of Breast Carcinoma Events in Patients with Ductal Carcinoma in Situ Treated with Breast-Conserving Surgery and Radiation Therapy with or without Tamoxifen Therapy^a

Breast CA event ^b	No. of patients (%)		Relative risk	P value
	Placebo (n = 899)	Tamoxifen (n = 899)		
All	153 (16.9)	100 (10.3)	0.63	0.0003
Ipsilateral	100 (11.1)	72 (7.7)	0.69	0.02
Invasive	49 (5.3)	27 (2.6)	0.53	0.01
Noninvasive	51 (5.8)	45 (5.0)	0.85	0.48
Contralateral	45 (4.9)	25 (2.3)	0.53	0.01
Invasive	30 (3.2)	20 (1.8)	0.64	0.16
Noninvasive	15 (1.7)	5 (0.5)	0.32	0.03

^a See Fisher et al., 2001.⁷

^b Overall, there was a 48% reduction in the cumulative incidence of all invasive breast carcinomas (8.5% vs. 4.4%; $P = 0.0009$).

with radiation therapy is associated with a higher rate of local recurrence, with approximately 50% of all recurrences being invasive.³ Because of these findings and because it has been shown that tamoxifen decreases the incidence of ipsilateral and contralateral breast tumors in patients with invasive breast carcinomas,^{4,5} the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 study was designed to investigate the value of adjuvant tamoxifen therapy after breast-conserving surgery in patients with DCIS.

In the NSABP B-24 study, 1804 women with DCIS who underwent lumpectomy and received 50 grays (Gy) of radiation were assigned randomly in a double-blind, placebo-controlled fashion to receive tamoxifen (20 mg daily) or placebo for 5 years.⁶ At a median follow-up of 83 months, as of June 2000, the administration of tamoxifen after lumpectomy and radiation therapy had resulted in a significant decrease in the 7-year cumulative incidence of all breast carcinoma events, particularly ipsilateral invasive carcinoma (Table 1).⁷ Although no survival benefit of tamoxifen use was shown, these findings led to U.S. Food and Drug Administration approval of tamoxifen for the adjuvant treatment of DCIS after surgery.

The influence of the results of the NSABP B-24 trial on physician recommendations regarding tamoxifen and patient utilization of tamoxifen remains unknown. The objective of the current study was to evaluate the impact of the B-24 study on current practices at a comprehensive cancer center.

MATERIALS AND METHODS

After obtaining approval from the Institutional Review Board of The University of Texas M. D. Anderson

Cancer Center (M. D. Anderson), the M. D. Anderson records (including all outside health care correspondences) of all 350 consecutive patients with an initial diagnosis of DCIS by core needle biopsy or excisional biopsy who were treated at the study institution between July 1999 (1 month after the results of NSABP B-24 were published) and June 2002 were obtained from a prospective database and analyzed. All prereferral pathology slides were reviewed at M. D. Anderson. All patients underwent surgical treatment for DCIS and had documented follow-up. Patients were excluded if the final surgical pathology review revealed invasive carcinoma.

Documented discussions regarding the use of tamoxifen after surgery for DCIS and whether tamoxifen was offered to patients were recorded. If tamoxifen was not offered, then the reason for not offering tamoxifen was recorded. If a patient was offered tamoxifen and declined tamoxifen, then the reason for declining tamoxifen was recorded. The duration of tamoxifen use, complications and side effects related to tamoxifen use, and compliance with tamoxifen use also were recorded.

Clinical and pathologic factors were evaluated for their impact on recommendations regarding tamoxifen. The clinical factors examined included age; race; menopausal status; family history of a first-degree relative with breast carcinoma; history of atypical ductal hyperplasia (ADH), lobular carcinoma in situ (LCIS), or invasive carcinoma; history of coronary artery disease, deep venous thrombosis, or pulmonary embolism; history of hysterectomy; history of hormone replacement therapy or previous tamoxifen or raloxifene use; and type of surgery. The pathologic factors evaluated included DCIS size, histologic grade, associated LCIS or ADH, the presence of necrosis, and surgical margin status. Estrogen receptor (ER) and progesterone receptor status were not evaluated routinely until 2002.

Statistical Analysis

Descriptive statistics were evaluated to assess the frequency distribution among patients who were or were not offered tamoxifen. Differences in the distribution of characteristics were analyzed with the Pearson chi-square test or the Fisher exact test. The differences between the medians of continuous variables were tested by the Mann-Whitney U test. Two-sided P values ≤ 0.05 were considered statistically significant. The SPSS 11.5 software package (SPSS Inc., Chicago, IL) was used for statistical analysis.

RESULTS

Of 350 patients who had an initial diagnosis of DCIS by core needle biopsy or excisional biopsy, 73 patients

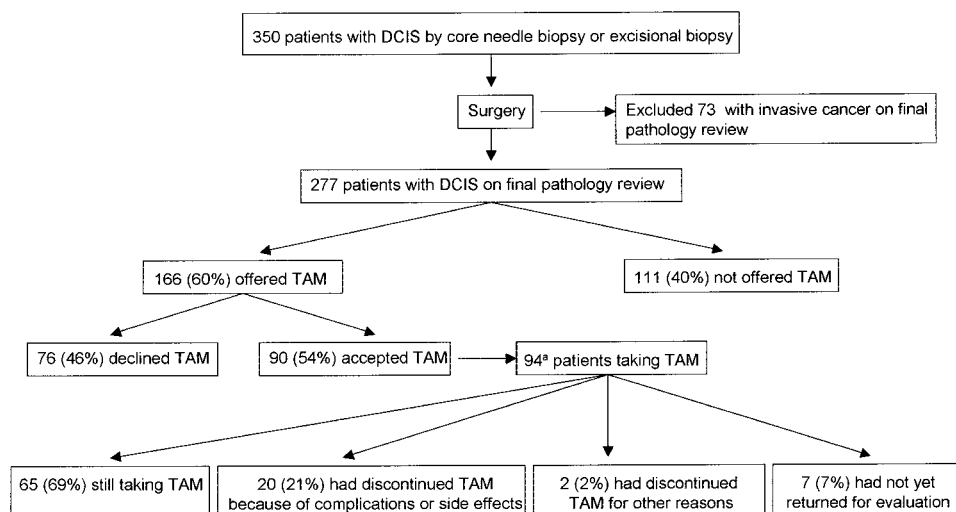


FIGURE 1. Tamoxifen (TAM) use in the 350 patients who were evaluated at The University of Texas M. D. Anderson Cancer Center between July 1999 and June 2002 with an initial diagnosis of ductal carcinoma in situ (DCIS) by core needle biopsy or excisional biopsy. *Includes four patients from the “not offered TAM” group who already were receiving TAM for other reasons.

were excluded from the current analysis because of evidence of invasive carcinoma on final pathology review (Fig. 1). Of the 277 patients who had DCIS on final surgical pathology review, 128 patients (46%) ultimately underwent total mastectomy; 149 patients (54%) underwent segmental mastectomy, including 114 patients (77%) who also received adjuvant radiation therapy. Of 277 patients, it was documented that 166 patients (60%) had been offered tamoxifen after surgery for DCIS, whereas 111 patients (40%) had not been offered tamoxifen. The rate of offering tamoxifen did not change over time. Between July 1999 through 2000, 77 of 124 patients (62%) were offered tamoxifen whereas from 2001 through June 2002, 89 of 153 patients (58%) were offered tamoxifen. For 72 of 111 patients (65%) who were not offered tamoxifen, the reason for not offering tamoxifen was not documented. For the remaining 39 patients, documented reasons were as follows: 25 patients had undergone bilateral mastectomies; 4 patients already were receiving tamoxifen for other reasons (history of invasive breast carcinoma in 3 patients and prophylaxis because of a strong family history of breast cancer in 1 patient); 2 patients already had completed 5 years of tamoxifen for previous invasive breast carcinomas; 1 patient (a postmenopausal woman) already was receiving anastrozole prior to her evaluation at M. D. Anderson; 1 patient had a concurrent, contralateral, invasive ER negative breast carcinoma; 2 patients had documented ER negative DCIS; and 4 patients had medical conditions that rendered tamoxifen use unfavorable (cardiac history requiring coronary bypass surgery or percutaneous angioplasty in 3 patients and history of stroke in 1 patient).

At a median follow-up of 13 months (range, 1 week to 38 months), 276 of 277 patients were without evidence of disease. The 1 remaining patient had a

recurrence of DCIS during adjuvant tamoxifen therapy 18 months after undergoing segmental mastectomy and receiving radiation therapy.

Patient Utilization of Tamoxifen

Of 166 patients who were offered tamoxifen, 90 patients (54%) agreed to take it, and 76 patients (46%) declined. Fifty of 76 patients (66%) who declined tamoxifen did not have documented reasons. Of the remaining 26 patients who declined tamoxifen, 22 patients feared the side effects of tamoxifen, 2 patients wanted to bear children, 1 patient had a history of a deep venous thrombosis, and 1 patient had a history of a transient ischemic attack.

Tamoxifen-Related Complications and Side Effects

Of 277 patients who had DCIS on final surgical pathology review, a total of 94 patients (34%) took tamoxifen. This group included the 90 patients who agreed to take tamoxifen after their diagnosis of DCIS and the additional 4 patients who already were taking tamoxifen for other reasons at the time of their initial evaluation at M. D. Anderson. At last follow-up, 66 of 94 patients (70%) had no documented complications from tamoxifen use, 7 patients (7%) had not yet been seen since tamoxifen was initiated, and 21 patients (22%) had documented complications or side effects that may have been related to tamoxifen use. The complications were elevated liver function tests, prompting the discontinuation of tamoxifen 8 months after initiation ($n = 1$ patient); lower-extremity phlebitis but no evidence of deep venous thrombosis, prompting the discontinuation of tamoxifen 6 months after initiation ($n = 1$ patient); and transient ischemic attack ($n = 1$ patient). The patient who had a transient ischemic attack underwent carotid endarterectomy for a high-grade carotid stenosis and remained on tamox-

ifen at last follow-up. Tamoxifen-related side effects that resulted in the discontinuation of tamoxifen were hot flashes, fatigue, and weight gain (eight patients); vaginal bleeding or discharge (three patients); nausea (two patients); and vertigo and visual disturbances (one patient). Four patients discontinued tamoxifen without documented reasons. The median duration of tamoxifen use in the 20 patients who discontinued tamoxifen was 3.5 months (range, 1–9 months).

Compliance with Planned Tamoxifen Therapy

At last follow-up, 65 of 94 patients (69%) who received tamoxifen therapy still were receiving tamoxifen, 20 patients (21%) had stopped taking tamoxifen because of side effects or complications, 2 patients (2%) had discontinued tamoxifen for other reasons, and 7 patients (7%) had not yet returned for evaluation since tamoxifen was initiated (Fig. 1). One of the two patients who stopped taking tamoxifen for reasons that were not related to complications or side effects had been receiving tamoxifen prophylaxis because of a strong family history of breast carcinoma. She underwent total mastectomy for DCIS as well as contralateral prophylactic mastectomy, and tamoxifen was discontinued subsequently. The second patient, who also had a family history of breast carcinoma, underwent segmental mastectomy, received radiation therapy, and received tamoxifen for DCIS. She underwent prophylactic laparoscopic hysterectomy and bilateral salpingo-oophorectomy 19 months later, and tamoxifen was discontinued subsequently.

Factors Affecting Recommendations Regarding Tamoxifen

The 277 patients with DCIS in the current study were evaluated by 8 different breast surgeons. The proportion of patients for whom tamoxifen was offered was surgeon dependent ($P = 0.009$), ranging from 14% to 73%. The clinicopathologic features of patients who were and were not offered tamoxifen are summarized in Table 2. It is noteworthy that 27 patients had a previous history of breast carcinoma, 10 in the group that was offered tamoxifen and 17 in the group that was not offered tamoxifen. Of the 17 patients who were not offered tamoxifen, 7 patients had undergone bilateral mastectomies, 3 patients already were receiving tamoxifen for their breast carcinoma, 2 patients had completed 5 years of tamoxifen, 1 patient had an ER negative breast carcinoma, 1 patient had a history of a stroke, and 3 patients had no documented reason why tamoxifen was not offered.

On univariate analysis, only two factors were found to be associated with recommendations for tamoxifen use. Patients who underwent segmental resection versus patients who underwent total mastec-

tomy ($P = 0.002$), and patients with smaller pathologic DCIS tumors ($P = 0.001$) were more likely to be offered tamoxifen. Further analysis revealed that these two factors were interrelated, because DCIS size is a confounding variable for type of surgery. The median pathologic size of DCIS in patients who underwent segmental mastectomy was 0.9 cm (range, 0.04–5.0 cm; $n = 107$ patients), and the median pathologic size of DCIS in patients who ultimately underwent total mastectomy was 2.0 cm (range, 0.2–10.0 cm; $n = 93$ patients). Thus, patients who had smaller tumors were more likely to undergo a segmental mastectomy and be offered tamoxifen; whereas patients with larger tumors were more likely to require total mastectomy for negative margins and, thus, were less likely to be offered tamoxifen. Multivariate analysis was not performed given the interrelation between these two factors.

DISCUSSION

The initial results of the NSABP B-24 trial were published in June 1999. At a median follow-up of 74 months, tamoxifen was reported to have reduced the absolute occurrence of ipsilateral and contralateral breast carcinoma events by 3.3% and 1.4%, respectively, after breast-conserving surgery and radiation therapy for DCIS.⁶ In September 1998, the results of the NSABP Breast Cancer Prevention Trial (P-1) were published. At a median follow-up of 55 months, women who were at increased risk for breast carcinoma who took 5 years of tamoxifen therapy had a 49% reduction in their risk of invasive breast carcinoma, which was confined to ER positive tumors (22.0 vs. 43.4 cases per 1000 women; $P < 0.00001$), and had a 50% reduction in the risk of noninvasive breast carcinoma (7.7 vs. 15.9 cases per 1000 women; $P < 0.002$).⁸ Patients who had a history of DCIS were not included in the P-1 study, because the NSABP B-17 study investigating the role of radiation therapy after lumpectomy for patients with DCIS also was open to enrollment. However, the results of both the B-17 study and the B-24 study indicated that patients with DCIS who underwent breast-conserving surgery followed by radiation therapy were at higher risk for developing invasive breast carcinoma compared with women who had a history of LCIS or ADH who were included in the P-1 study, thereby further supporting the possible benefits of adjuvant tamoxifen therapy in patients with DCIS.^{6,9,10}

The P-1 trial also confirmed the findings of previous studies^{11,12} that patients taking tamoxifen had an increased rate of endometrial carcinoma and thromboembolic events, especially among women age > 50 years (Table 3), and had increases in vasomotor symptoms (hot flashes and vaginal discharge or bleeding),

TABLE 2
Clinicopathologic Features of Patients Offered and Not Offered Tamoxifen^a

Feature	No. of patients (%)		P value ^b
	Offered TAM (n = 166 patients)	Not offered TAM (n = 111 patients)	
Age (yrs)			0.394 ^c
Median	56	56	
Range	33–82	24–89	
Race			0.105
White	116 (70)	86 (78)	
Hispanic	28 (17)	13 (11)	
African-American	10 (6)	10 (9)	
Asian	11 (7)	1 (1)	
Indian	1 (0.6)	1 (1)	
Menopausal status			0.051
Premenopausal	39 (24)	38 (34)	
Postmenopausal	127 (76)	73 (66)	
Family history of breast CA	22 (13)	21 (19)	0.205 ^d
History of LCIS or ADH	5 (3)	3 (3)	1.0 ^e
Previous history of breast CA	10 (6)	11 (10) ^f	0.231
History of hysterectomy	53 (32)	34 (31)	0.820
History of thromboembolic event	3 (2)	1 (1)	0.652 ^e
Pathologic size of DCIS (cm)			0.001 ^c
Median	1.0	1.7	
Range ^g	0.04–10.0	0.2–10.0	
High histologic grade	72 (43)	51 (46)	0.673
Presence of necrosis	106 (64)	77 (69)	0.328 ^d
Associated LCIS or ADH in specimen	51 (31)	32 (29)	0.736
Negative margin	166 (100)	111 (100)	NA
Palpable tumor	21 (13)	16 (14)	0.716 ^d
Type of final surgery			0.002
Segmental mastectomy	102 (61)	47 (42)	
Total mastectomy	64 (39)	64 (58)	

TAM: tamoxifen; CA: carcinoma; LCIS: lobular carcinoma in situ; ADH: atypical ductal hyperplasia; DCIS: ductal carcinoma in situ; NA: not applicable.

^a Values in the table represent the number of patients (%) unless otherwise specified.

^b P value was calculated by Pearson chi-square test unless otherwise noted.

^c P value was calculated by Mann-Whitney U test.

^d Excludes patients with unknown values.

^e P value was calculated by Fisher exact test.

^f Seventeen patients with a previous history of breast carcinoma were not offered tamoxifen. Six patients were excluded from the analysis, including 3 patients who already were receiving tamoxifen for breast carcinoma, 2 patients who had completed 5 years of tamoxifen for previous breast carcinoma, and 1 patient who had breast carcinoma with negative estrogen receptor status.

^g Based on 119 patients who were offered tamoxifen and 81 patients who were not offered tamoxifen for whom the size of the ductal carcinoma in situ was known.

cataract formation, and the need for cataract surgery. Furthermore, 24% of patients taking tamoxifen discontinued therapy during the study period.⁸ Other documented side effects of tamoxifen include ocular disturbances, hepatic toxicity (elevated liver enzyme levels, hepatitis, and cholestasis), increased risk for uterine sarcoma, skin rash, anemia, leukopenia, thrombocytopenia, neutropenia, and elevated triglyceride levels.^{13–15}

Thus, for women with DCIS, tamoxifen provides risk reduction in the ipsilateral breast in women who undergo breast-conserving surgery as well as in the contralateral breast in women who undergo mastectomy or breast-conserving surgery. However, the over-

all combined absolute risk reduction of 5% with tamoxifen therapy is quite small. Furthermore, no survival advantage with tamoxifen use has been demonstrated, and tamoxifen use has a significant side-effect/complication profile. Therefore, the benefits and risks of tamoxifen use must be considered carefully in patients after they undergo surgery for DCIS.

To the best of our knowledge, there have been only two analyses investigating actual physician recommendations regarding tamoxifen and patient utilization of tamoxifen after surgery for DCIS at a comprehensive cancer center since the publication of the B-24 and P-1 studies. In an abstract reported by Morrow et al.¹⁶ in 2003, patients with DCIS or invasive

TABLE 3
National Surgical Adjuvant Breast and Bowel Project P-1: Average Annual Rates of Invasive Endometrial Carcinoma and Vascular-Related Events in Patients with or without Tamoxifen Therapy^a

Event type by age at entry	Rate per 1000 women		Risk ratio	95% CI
	Placebo	Tamoxifen		
Invasive endometrial carcinoma	0.91	2.30	2.53	1.35-4.97
Age ≤ 49 yrs	1.09	1.32	1.21	0.41-3.60
Age ≥ 50 yrs	0.76	3.05	4.01	1.70-10.90
Pulmonary embolism	0.23	0.69	3.01	1.15-9.27
Age ≤ 49 yrs	0.10	0.20	2.03	0.11-119.62
Age ≥ 50 yrs	0.31	1.00	3.19	1.12-11.15
Deep venous thrombosis	0.84	1.34	1.60	0.91-2.86
Age ≤ 49 yrs	0.78	1.08	1.39	0.51-3.99
Age ≥ 50 yrs	0.88	1.51	1.71	0.85-3.58
Stroke	0.92	1.45	1.59	0.93-2.77
Age ≤ 49 yrs	0.39	0.30	0.76	0.11-4.49
Age ≥ 50 yrs	1.26	2.20	1.75	0.98-3.20

95% CI: 95% confidence interval.

^a See Fisher et al., 1998.⁸

carcinoma were more likely to be offered tamoxifen therapy compared with patients who had either atypia or LCIS. Overall, 72% of their patients at high risk for breast carcinoma were offered tamoxifen, 62% of whom accepted tamoxifen therapy. In the current study, we found that only 60% of all patients (166 of 277 patients) with DCIS on final surgical pathology review were offered tamoxifen and that there was specific clinician variability with respect to the offering of tamoxifen ($P = 0.009$). Based on these results, our current policy is to discuss the option of tamoxifen therapy and the absolute risk and benefits of this approach for all patients with DCIS. Of all the clinicopathologic factors investigated, only two were associated with recommendations for tamoxifen use after surgery for DCIS: patients who underwent segmental resection (vs. total mastectomy) and patients with smaller pathologic DCIS tumors were more likely to be offered tamoxifen. In addition, these two factors were interrelated. Patients with smaller tumors were more likely to undergo segmental mastectomy and to be offered tamoxifen whereas patients with larger tumors were more likely to require total mastectomy for negative margins and, thus, were less likely to be offered tamoxifen. Sixty-eight percent of patients who underwent segmental mastectomy as their final surgery were offered tamoxifen, and 50% of patients who underwent total mastectomy as their final surgery were offered tamoxifen. Thus, tamoxifen was offered for both ipsilateral and contralateral breast carcinoma risk reduction.

It has been established that tamoxifen use is as-

sociated with an increased rate of endometrial carcinoma, especially in postmenopausal women.⁸ Therefore, the finding that postmenopausal women were more likely to be offered tamoxifen was unexpected. This result may be related to clinician-perceived, severe, negative effects of antiestrogen therapy in younger women compared with postmenopausal women. Furthermore, it was surprising that a history of hysterectomy did not appear to influence the rate of offering tamoxifen in the current study. The actual reasons for these findings remain to be elucidated.

We also found that 46% of patients who were offered tamoxifen declined therapy, with the most common documented reason being fear of possible tamoxifen-related side effects or complications. Of the initial 277 patients in the current study, only 34% received tamoxifen therapy. Furthermore, because of a high discontinuation rate (21%) due to tamoxifen-related side effects and complications, at last follow-up, only 23% of the initial 277 patients still were taking tamoxifen.

There were some limitations to the current study. First, there are inherent potential limitations to any single-institution study. Notwithstanding those potential limitations, the results of the current study may be valuable to other institutions with respect to their own recommendations and patient acceptance of chemoprevention in this particular clinical setting. This type of critical analysis from a very large, comprehensive cancer center provides insight into the complexities of this decision-making process for both clinicians and patients. The fact that our group performed this type of analysis opens this issue to critical analysis and debate among other cancer experts and may be useful for the design of prospective trials for chemoprevention of breast carcinoma in patients with DCIS. Second, although we routinely follow all patients on tamoxifen therapy and have reviewed all outside health care correspondences for this study, it is possible that we have underestimated the actual discontinuation rate, complications, and side effects of tamoxifen if this information was not included in the medical record.

We did not determine ER status or progesterone receptor status routinely in our patients with DCIS until 2002, as stated earlier. Allred et al. recently reported their results from 628 patients with DCIS in the NSABP B-24 study for whom ER status was known.¹⁷ Of those 628 patients, 482 patients (77%) had ER positive DCIS. At a median follow-up of 104 months, tamoxifen use resulted in a 59% reduction in the incidence of all breast carcinoma events (ipsilateral and contralateral) in patients with ER positive tumors ($P = 0.0002$) and in a 20% reduction in the risk of all breast carcinoma events in women with ER negative

tumors ($P = 0.51$). These data suggest that the ER status of patients with DCIS should be determined routinely, because ER expression may be an important predictor of response to tamoxifen. On the basis of these initial results from Allred et al., we now routinely use ER status to select patients with DCIS who would have the greatest potential to benefit from tamoxifen.

Tamoxifen is a selective ER modulator that binds the ER, ultimately affecting gene transcription.^{18,19} This results in the well known antagonist properties of tamoxifen but also accounts for its partial agonist properties, which may be responsible for some of its detrimental side effects.^{11,20} Because of the side-effect profile of tamoxifen and the subsequent reluctance of patients to accept tamoxifen therapy for chemoprevention,²¹ other agents have been introduced that may reduce breast carcinoma events, may increase overall survival in women with early-stage breast carcinoma or DCIS, and may have fewer side effects compared with the side effects seen with tamoxifen. These agents include aromatase inhibitors, such as anastrozole; raloxifene,^{22–24} a selective ER modulator with less uterine agonist activity than tamoxifen; sulfatase inhibitors; gonadotropin-releasing hormone agonists; ER down-regulators; retinoids and rexinoids; and selective cyclooxygenase-2 inhibitors (celecoxib).²⁵

Aromatase inhibitors inhibit estrogen synthesis in the peripheral tissues by blocking the final conversion of androgen to estrogen, thereby reducing the amount of circulating estrogen.^{26,27} Anastrozole, a third-generation nonsteroidal aromatase inhibitor, is tolerated well and is superior to tamoxifen with respect to time to disease progression when used as a first-line treatment for patients with advanced breast carcinoma.^{28–32} In addition, initial results of the Anastrozole, Tamoxifen, Alone or in Combination trial, published in June 2002, demonstrated that, for postmenopausal women with early-stage, operable, hormone –receptor-positive breast carcinoma, at a median follow-up of 33.3 months, disease-free survival at 3 years was superior for women who were treated with anastrozole compared with women who were treated with tamoxifen ($P = 0.013$).³³ Furthermore, compared with patients who were treated with tamoxifen, patients who were treated with anastrozole had a significantly lower incidence of contralateral breast carcinoma ($P = 0.007$) and had significantly fewer side effects and complications. The combination of anastrozole and tamoxifen was not associated with improved survival or tolerability compared with tamoxifen alone.

On the basis of these findings, the NSABP recently opened protocol NSABP B-35, a study that was designed to test the hypothesis that inhibition of estrogen production with an aromatase inhibitor will delay

the progression of disease or reduce the risk of recurrence of DCIS with fewer complications than are seen with tamoxifen. In that study, approximately 3000 postmenopausal women with hormone –receptor-positive DCIS who are treated with lumpectomy and radiation therapy will be randomized to receive either tamoxifen (20 mg daily) or anastrozole (1 mg daily) for 5 years. Endpoints of evaluation will include breast carcinoma events (ipsilateral, contralateral, invasive, noninvasive, regional, and distant), quality of life and symptoms, disease-free survival, overall survival, and quality-adjusted survival.

The findings of the current study demonstrated that both physicians and patients at a comprehensive cancer center remained cautious regarding the use of tamoxifen after surgery for DCIS after the publication of the NSABP B-24 findings in June 1999. Physician recommendations for tamoxifen use after surgery for DCIS may be influenced in part by the lack of compelling data regarding a large absolute risk reduction and no reported survival advantage with tamoxifen therapy. Furthermore, patient reluctance to accept tamoxifen likely is related to each individual's perceived risk for breast carcinoma compared with their perceived risk for tamoxifen-related complications and side effects. These findings confirm the importance of future trials evaluating alternative chemopreventive strategies for patients with DCIS. Currently, at M. D. Anderson, in accordance with the National Comprehensive Cancer Network guidelines,³⁴ tamoxifen use is not a mandatory part of adjuvant treatment for DCIS. The decision to take tamoxifen after undergoing either breast-conserving surgery or total mastectomy for DCIS is based largely on the clinical assessment of potential individual risks and benefits. The decision to take tamoxifen after surgery for DCIS should be made on a patient-by-patient basis. On the basis of the results of the current study, we strongly advocate discussion of the risks and potential benefits of participating in NSABP B-35 or other chemoprevention trials for DCIS. For patients who may not be eligible to participate in ongoing trials, we strongly encourage discussion of the risks and potential benefits of taking tamoxifen after surgery for DCIS.

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