Tamoxifen is commonly used in the management of patients with breast cancer. Clinical trials of tamoxifen involving over 75,000 patients demonstrate an improved recurrence-free and overall survival benefit in both pre- and post-menopausal women. Large-scale trials also are evaluating the role of tamoxifen as a chemopreventive agent in women considered to be at high risk for developing breast cancer based on family history. Endometrial cancer is an uncommon complication of tamoxifen therapy. Since the majority of these cancers will be detected at an early stage when they are highly curable, however, the overall benefit of tamoxifen treatment in breast cancer patients outweighs this risk. All women receiving tamoxifen who have a uterus should undergo regular gynecologic examinations.

Introduction

Tamoxifen, a nonsteroidal antiestrogen, has been widely used since the 1970s in the management of patients with breast cancer. It is believed to work by blocking the binding of estrogen to the estrogen receptor. Although primarily an antiestrogen, tamoxifen also may exhibit some mild estrogenic effects. Following the initial report by Killackey et al[1] that suggests a possible link between tamoxifen use and the development of endometrial carcinoma in three patients, approximately 200 additional cases of tamoxifen-associated uterine cancer have been reported.[2-14] The recent results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 randomized trial of tamoxifen vs placebo in women with estrogen receptor-positive breast cancer confined to the breast with negative axillary nodes revealed a 7.5-fold increase in the risk of developing endometrial cancer in the tamoxifen-treated group.

The indications for tamoxifen use have broadened to include long-term adjuvant therapy as well as chemoprophylaxis for selected high-risk women. Consequently, a large number of women, including healthy young patients with no history of cancer, will be subjected to the long-term effects of tamoxifen. This review evaluates the current literature regarding tamoxifen use in breast cancer patients and associated uterine neoplasia including endometrial carcinomas and sarcomas. The potential role of screening for endometrial cancer in tamoxifen-treated breast cancer patients also is discussed.

Endometrial Carcinoma

In the 1980s, several preclinical studies indicated that tamoxifen may exert an estrogenic effect on the endometrium. Satyaswaroop et al[16] transplanted both estrogen receptor-positive and estrogen receptor-negative human endometrial cancer cell lines into nude mice and evaluated the effects of both tamoxifen and 17 beta-estradiol on tumor growth. Although the estrogen receptor-negative tumor grew rapidly, there was no difference in the rate of tumor growth between tamoxifen or estrogen-treated animals compared with controls. In contrast, the rate of growth of the estrogen receptor-positive cell line was significantly accelerated in the tamoxifen-treated animals compared with controls, although to a lesser degree than was seen with estrogen treatment. Tamoxifen also increased the levels of functional progesterone receptors, lending further evidence to the estrogenic potential of tamoxifen. Gottardis et al[17] demonstrated in athymic mice the contrasting actions of tamoxifen on the growth of estrogen receptor-positive breast and endometrial cancer cell lines. While stimulating the growth of the endometrial tumor, tamoxifen had no effect on the breast tumor growth and had an antagonistic action on the estradiol-stimulated growth of breast tumors.

The estrogenic effect of tamoxifen on the female genital tract also has been demonstrated clinically. Boccardo et al[18] investigated the estrogen-like effect of tamoxifen on the vaginal epithelium. Hormonal evaluation can be determined by means of exfoliative vaginal cytology using the karyopyknotic index (KPI), which is the relation of mature superficial cells to intermediate cells. Postmenopausal estrogen replacement therapy generally induces increased cellular maturity and consequently increases the KPI. Following tamoxifen treatment of at least eight weeks, these researchers noted a significantly higher KPI than for untreated patients, suggesting an estrogenic effect of tamoxifen on the vaginal epithelium.

In 1985, Killackey et al[1] suggested a possible link between tamoxifen and endometrial cancer when they reported three such cancers occurring in breast cancer patients with a prior history of tamoxifen use. While not conclusively providing evidence for tamoxifen-induced endometrial cancer, this and other anecdotal reports spurred researchers to more closely evaluate the link between antiestrogens and the subsequent development of uterine neoplasia. The strongest data linking the use of tamoxifen with the development of endometrial cancer were published in 1989 by Fornander et al.[4] The authors reviewed the frequency of new primary cancers as recorded in the Swedish Cancer Registry for a group of 1,846 postmenopausal women with early breast cancer who were included in a randomized trial of adjuvant tamoxifen. They noted a 6.4-fold increase in the relative risk of endometrial cancer in 931 tamoxifen-treated patients, compared with 915 patients in the control group. The dose of tamoxifen in this study was 40 mg/d (double the conventional dose used in the United States), and the greatest cumulative risk of developing endometrial cancer occurred after five years of tamoxifen use.

Results from NSABP B-14 confirmed the association between tamoxifen use and the development of endometrial cancer.[12] Data regarding the rates of endometrial and other cancers were analyzed on 2,843 patients with node-negative, estrogen receptor-positive, invasive breast cancer randomly assigned to placebo or tamoxifen (20 mg/d) and on 1,220 tamoxifen-treated patients registered in NSABP B-14 subsequent to randomization. Two of the 1,424 patients assigned to receive placebo developed endometrial cancer; however, both had subsequently received tamoxifen for treatment of breast cancer recurrence. Fifteen patients randomized to tamoxifen treatment developed endometrial cancer. One of these patients never actually accepted tamoxifen therapy. Eight additional cases of uterine cancer occurred in the...
The average annual hazard rate for endometrial cancer in the placebo group was 0.2:1000, compared with 1.6:1000 for the randomized, tamoxifen-treated group. The relative risk of an endometrial cancer occurring in the randomized, tamoxifen-treated group was 7.5:1000. Similar results were seen in the 1,220 registered patients who received tamoxifen. No imbalance was seen between the treatment groups in the number of patients having undergone prior hysterectomy, although the exact percentage of these patients was not stated. Assuming that approximately 30% of the patients in the tamoxifen-treated group had undergone prior hysterectomy, the annual hazard rate for endometrial cancer probably is closer to 1.6:700 (0.2%). Based on these results, clinicians may counsel their patients on tamoxifen that the annual risk of developing endometrial carcinoma is approximately 1:1000 (0.2%). However, the risks of tamoxifen-induced endometrial cancer must be weighed against the benefits of tamoxifen in reducing breast cancer recurrence and new contralateral breast cancers. In the B-14 trial, the cumulative rate per 1,000 population of breast cancer relapse was reduced from 227.8 in the placebo group to 123.5 in the randomized tamoxifen-treated group. In addition, the cumulative rate of contralateral breast cancer was reduced from 40.5 to 23.5 per 1000, respectively, in the two groups. Taking into account the increased cumulative rate of endometrial cancer, there was a 38% reduction in the five-year cumulative hazard rate in the tamoxifen-treated group. These results led the authors to conclude that the benefit of tamoxifen therapy for breast cancer outweighs the potential increase in endometrial cancer reported.

Recent results from three large Scandinavian breast cancer trials have further confirmed the relationship between tamoxifen use and the development of endometrial cancer. These studies, which included a total of 4,914 patients with a median follow-up of eight to nine years, were analyzed for the occurrence of second primary cancers. Increases in endometrial cancers among the tamoxifen-treated patients were statistically significant [RR= 4.1].

**Histology and Prognosis of Tamoxifen-Induced Endometrial Cancer**

The etiology of tamoxifen-associated endometrial neoplasia has not been established. One hypothesis is that some metabolites of tamoxifen may act primarily as estrogen agonists, which may lead to the development of endometrial neoplasia. Metabolite E, for example, which is formed by the removal of the aminomethane side chain from tamoxifen, is a weakly estrogenic compound that binds the estrogen receptor with low affinity.[19] The clinical significance of this and other metabolites of tamoxifen remains to be determined.

Unopposed estrogen administration is associated with an increased risk for endometrial carcinoma. The predominant risk is the development of early-stage, low-grade, minimally invasive lesions that have a favorable prognosis.[20] If tamoxifen were to be exerting weakly estrogenic activity on the endometrium, associated endometrial cancers could be expected to have clinical characteristics comparable to those associated with unopposed estrogen. Some authors have suggested that uterine cancers occurring in breast cancer patients taking tamoxifen may behave more aggressively and carry a poorer prognosis. In a recent report from the Yale Tumor Registry,[8] 53 patients were identified with invasive or in situ breast cancer and subsequently developed uterine cancer. Fifteen of the patients received adjuvant tamoxifen at a dose of 40 mg/d for a mean of 4.2 years, while 38 had not received tamoxifen. The mean patient age was 72.3 years for tamoxifen users, which was not statistically different from those not receiving tamoxifen (68.5 years). The interval between the diagnosis of breast and endometrial cancer was significantly lower in the tamoxifen-treated group compared with those not receiving tamoxifen (5.3 vs 12.3 years). Fifty-seven percent of uterine cancers occurring in the tamoxifen-treated patients had high-grade lesions (grade 3 adenocarcinoma) or high-risk histologies (papillary serous, clear cell, mixed mesodermal tumor) compared with 28% of those developing in the 38 breast cancer patients who had not received tamoxifen. In addition, patients in the tamoxifen-treated group were statistically more likely to die of endometrial cancer (33.3% vs 26%). These findings led the authors to conclude that endometrial cancers occurring after tamoxifen therapy may behave more aggressively and carry a poorer prognosis than those occurring in patients who had not received tamoxifen. In addition, the presence of a high percentage of poor-prognosis histologies, including poorly differentiated adenocarcinoma, papillary serous, and clear cell cancers, as well as mixed mesodermal tumors in the tamoxifen-treated group, led the authors to speculate that the mechanism of tamoxifen-induced endometrial neoplasia may be different from that of exogenous estrogen, which is associated with more favorable histologies.

Silva et al.[14] reviewed the data from M.D. Anderson Cancer Center of 72 breast cancer patients who subsequently developed malignant uterine neoplasms. Fifty-seven patients had not received tamoxifen as part of their treatment while 15 patients had. Among the tamoxifen-treated patients, 33% of the tumors had papillary serous histology, which was significantly higher than the 7% incidence occurring in patients who had not received tamoxifen. No mention is made by the authors, however, as to the type or duration of chemotherapy given to either group of patients for treatment of their breast cancer. A high incidence of leiomyosarcomas was noted in both tamoxifen-treated and untreated patients (14% vs 17%), which is much higher than the 1% to 2% incidence of sarcomas that one would expect. Other reports of uterine sarcomas occurring in tamoxifen-treated breast cancer patients have been published, but these essentially consist of anecdotal case reports.

Several recent studies[11-13, 21] have documented that the type and prognosis of endometrial cancers that develop during or after tamoxifen therapy are no different from endometrial cancers occurring in the general population. In a study[13] from the Memorial Sloan-Kettering Cancer Center of 73 patients with a history of breast cancer who subsequently developed uterine cancer, 23 (32%) had received tamoxifen for at least one year, with a median duration of use of 4.5 years, while 50 (68%) did not receive tamoxifen. There was no significant difference in age, mean weight, or median survival following hysterectomy between the two groups of patients. The median interval between diagnosis of breast and uterine cancer was less in those receiving tamoxifen (4.6 vs 6.7 years), but this was not statistically significant. There was no significant difference in the FIGO stage of uterine cancers occurring in patients who had received tamoxifen compared with nonusers. Of the corpus cancers occurring in the tamoxifen-treated group, 74% were endometrial adenocarcinomas, while 26% consisted of high-risk histologic subtypes, including papillary serous and clear cell carcinomas, as well as uterine sarcomas. This distribution was identical to that seen in the group not receiving tamoxifen. Five women (22%) from the tamoxifen group died of uterine cancer, as did 13 (26%) of those who did not receive tamoxifen. The study concluded that there was no difference in the stage, grade, or histologic subtype of corpus cancers that develop in breast cancer patients based on tamoxifen use.

Similar results have been reported in other studies. Forndner et al.[21] recently reported the clinicopathologic findings of endometrial cancers occurring as second primaries in 931 tamoxifen-treated patients with early breast cancer from the Stockholm Adjuvant Tamoxifen Trial.4 The median duration of tamoxifen use was 24 months, and the dose was 40 mg/d. On histologic review of these cancers, 82% were FIGO stage I, and all were histologic grade 1 or 2. Three deaths (18%) were attributed to cancer. The results of a case-control study from the Netherlands Cancer Registry were reported recently by van Leeuwen et al.[11] No difference was seen in the FIGO stage or histologic distribution of endometrial cancers that occurred in 23 breast cancer patients who received tamoxifen compared with 75 who did not. No tamoxifen-treated patients died of endometrial cancer compared with four who did not receive tamoxifen. Finally, the results of the NSABP B-14 trial[12] confirmed that uterine cancers occurring in tamoxifen-treated breast cancer patients are not associated with a higher incidence of adverse histologic features. Of the tamoxifen-associated endometrial cancers, 88% were FIGO stage I. In addition, 71% were endometrioid adenocarcinomas, and 78% were low-grade lesions. Four deaths (16.7%) were due to endometrial cancer.

**Screening for Endometrial Cancer**

**Endometrial Sampling**
To date, there is no proven method of screening for endometrial cancer in breast cancer patients on tamoxifen. The expected annual risk of endometrial cancer in these patients is approximately 2:1000 as defined by the B-14 trial.[12] A screening program may detect premalignant endometrial precursors, such as atypical hyperplasia, or benign endometrial conditions including polyps, the incidence of which will be higher than 2:1000. The best method for screening, however, remains to be determined. Some have proposed annual endometrial sampling, although this is associated with difficulties. Gal et al.[22] were unable to perform office endometrial biopsies with a Novak curette in 44% of 89 postmenopausal patients due to atrophic changes. Should asymptomatic patients who cannot undergo an office endometrial biopsy be subjected to the inherent morbidity of a fractional dilatation and curettage (D&C) under general anesthesia? Certainly all patients with abnormal bleeding should seek immediate gynecologic evaluation. As reported by Gibson et al.[23] all cases of endometrial carcinoma detected by D&C in tamoxifen-treated breast cancer patients presented with abnormal bleeding.

In a report[24] of the preliminary results of a prospective endometrial screening study in tamoxifen-treated breast cancer patients at the 1995 Annual Meeting of the American Society of Clinical Oncology, 126 patients with a mean age of 51 years were entered on the study. Six (4.8%) patients could not undergo the biopsy procedure due to a stenotic cervix, and of the remaining 120 patients, seven (5.8%) were noncompliant, four were removed from the study due to progression of breast cancer, four discontinued use of tamoxifen, and four were considered protocol violations. The remaining 101 evaluable patients underwent a total of 296 biopsies (mean 3), using a Pipelle endometrial biopsy device (Unimar; Wilmington, Conn), with a median surveillance time of 16.2 months. Four (4%) biopsies were abnormal (two complex hyperplasias, one atypical hyperplasia, and one with an abnormal amount of histiocytes). All abnormal biopsies were confirmed by fractional D&C. Six (6%) additional patients required D&C for persistent bleeding despite benign biopsies. The findings at D&C included polyps (three), normal (two), and pseudodecidualization (one). Of three patients undergoing hysterectomy, the first developed complex atypical hyperplasia following 12 months of tamoxifen. The second underwent a hysterectomy for a pelvic mass following 15 months of tamoxifen that on final pathology revealed a high-grade leiomyosarcoma. A third patient underwent hysterectomy for complex hyperplasia with extensive mucinous change after 13 months of tamoxifen. The authors concluded that office endometrial biopsies can be used to monitor the endometrium in the majority (95%) of breast cancer patients on tamoxifen. A D&C may be required for 6% of patients for persistent bleeding. Significant pathology was detected by endometrial biopsy in two (2%) patients and due to close surveillance in a third. However, longer follow-up will be required to determine the value of routine endometrial biopsies in tamoxifen-treated breast cancer patients.

Transvaginal Sonography

Transvaginal sonography may provide a noninvasive means of screening for endometrial pathology in tamoxifen-treated breast cancer patients. The definition of an abnormal endometrial stripe in tamoxifen-treated breast cancer patients remains undefined. Lahti et al.[9] reported that if a cutoff of >5 mm was used to define an abnormal endometrial echo, 22 (51.2%) patients had no abnormal endometrial pathology. Similar findings were reported by Cohen et al.[25] who prospectively performed endometrial biopsies following vaginal sonography in 72 tamoxifen-treated breast cancer patients. Among the patients with an endometrial stripe greater than 5 mm, approximately 70% had no identifiable endometrial tissue and only one patient was found to have endometrial cancer. Kedar et al.[26] reported a predictive value of 100% (16:16) for atypical hyperplasia or polyps with an endometrial stripe of >8 mm. These findings suggest that premalignant changes can be detected with transvaginal sonography, and the use of ultrasound and/or endometrial sampling to screen for endometrial neoplasia needs to be evaluated in large prospective trials before recommendations for screening can be made.

The ultrasonographic findings of the endometrium in tamoxifen-treated patients may be overinterpreted. Goldstein[27] recently reported five postmenopausal tamoxifen-treated patients who on routine surveillance with vaginal probe ultrasound were described as having heterogeneous, bizarre-appearing endometria with multiple sonoluent areas suggestive of a polyp. Because of concerns regarding tamoxifen use and endometrial neoplasia, the first patient was referred for a curettage and hysteroscopy. Minimal tissue was obtained and hysteroscopic evaluation revealed a smooth atrophic endometrium. When the abnormal sonographic appearance persisted, the patient underwent a sonohysterogram, which involves the instillation of 3 to 10 mL of saline at the time of sonography. The fluid enhancement revealed that the changes originally interpreted as endometrial were actually subendometrial in origin. Four additional patients with similar abnormal sonographic findings were found to have subendometrial abnormalities on sonohysterogram. It is unclear what these normal areas represent, as these patients have not undergone hysterectomy, although it was speculated that they may represent adenomyomatous-like changes. Further studies regarding the sonographic appearance of the endometrium in tamoxifen-treated patients are warranted.

The ultimate goal of any cancer screening program is to detect disease at an earlier stage when it is more curable. Since tamoxifen-associated endometrial cancers appear to have a similar stage, grade, and histology as endometrial cancers occurring in the general population, their prognosis is generally good, and early detection probably will not improve outcome significantly. A small number of tamoxifen-treated breast cancer patients could be expected to benefit from screening for endometrial cancer. Since the annual risk of endometrial cancer is 2:1000 in this population and approximately 15% of these cancers will result in death of the patient, annual screening could potentially decrease mortality in only 0.03% (0.002 X 0.15 = 0.0003) of all tamoxifen-treated breast cancer patients. The definition of an endometrial carcinoma in postmenopausal breast cancer patients remains undefined. Lahti et al.[9] reported that if a cutoff of >5 mm was used to define an abnormal endometrial echo, 22 (51.2%) patients had no abnormal endometrial pathology. Similar findings were reported by Cohen et al.[25] who prospectively performed endometrial biopsies following vaginal sonography in 72 tamoxifen-treated breast cancer patients. Among the patients with an endometrial stripe greater than 5 mm, approximately 70% had no identifiable endometrial tissue and only one patient was found to have endometrial cancer. Kedar et al.[26] reported a predictive value of 100% (16:16) for atypical hyperplasia or polyps with an endometrial stripe of >8 mm. These findings suggest that premalignant changes can be detected with transvaginal sonography, and the use of ultrasound and/or endometrial sampling to screen for endometrial neoplasia needs to be evaluated in large prospective trials before recommendations for screening can be made.

Conclusions

The mechanisms of tamoxifen-associated endometrial carcinogenesis remain undetermined. Chemical substances may exert their carcinogenic effect through a direct genotoxic mechanism; tamoxifen has been shown to cause DNA adduct formation in rodent liver.[28,29] Pongracz et al.[30] recently demonstrated that metabolite E of tamoxifen, which is found in the plasma of tamoxifen-treated patients, can be microsomal metabolically transformed into DNA adducts. In an evaluation[31] of the status of c-Ki-ras mutations in endometrial cancers occurring in breast cancer patients using DNA single-strand conformation polymorphism screening, a higher incidence of mobility shifts was noted that was consistent with mutation in the 15 tamoxifen-associated cancers compared with the 13 cancers that occurred in patients not receiving tamoxifen. These preliminary results need to be confirmed in a larger number of cases. In addition, it may be valuable to evaluate the status of other proto-oncogenes and tumor-suppressor genes in tamoxifen-associated endometrial cancers, as well as in endometrial cancers occurring in breast cancer patients who have not received tamoxifen. Studies such as these may ultimately increase our understanding of the mechanisms involved in tamoxifen-induced endometrial carcinogenesis.

References


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