

A RECONSIDERATION OF TAMOXIFEN USE FOR BREAST CANCER

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Tamoxifen, the first clinically available selective estrogen receptor modulator, was developed in 1966 and has been proven to be efficacious in all settings of breast cancer [1]. However, a series of case reports announced an association between tamoxifen therapy in women with breast cancer and the development of endometrial carcinoma in the mid-to-late 1980s [1]. In the previous issue of the *Taiwanese Journal of Obstetrics and Gynecology* [2], Dr Wu reported a rare case of secretory endometrial adenocarcinoma in a 71-year-old woman who was a victim of stage II breast cancer treated by mastectomy, chemotherapy, and 10-year daily tamoxifen. Adjuvant therapy with tamoxifen after breast cancer should be reconsidered because of the many possible side effects.

Tamoxifen has demonstrated special efficacy in the treatment and prevention of estrogen receptor (ER)-positive breast carcinoma [3,4]. Three randomized trials are prospectively evaluating tamoxifen (Nolvadex®; AstraZeneca, Wilmington, DE, USA) for breast cancer risk reduction [5–8]. The International Breast Cancer Intervention Study I (IBIS-I) trial showed a 25% reduction in the risk of invasive breast cancer with tamoxifen [9]. A meta-analysis of these studies, of which the National Surgical Breast and Bowel Project P-1 trial contributed the largest proportion of entered patients, identified a significant 42% reduction in relative risk (RR) of developing breast cancer associated with tamoxifen use (RR, 0.58; 95% confidence interval, CI, 0.38–0.84) [5]. The absolute risk reduction in these trials was less than 2 per 100 women given tamoxifen for 5 years [8]. The absolute risk reduction anticipated in an individual woman depends on her calculated breast cancer risk, with women at higher risk having greater potential benefit [9]. For example, the average

65-year-old woman with no family history has an anticipated risk reduction of 1 per 100, while a 50-year-old woman with two affected siblings and two prior biopsies but no germline mutation has an anticipated risk reduction of approximately 2.5 per 100. In an overview of data from 37,000 women with breast cancer from 55 trials of adjuvant therapy, the proportional reduction in recurrence was 47% after 5 years of treatment with tamoxifen and the proportional reduction in mortality was 26% after 10 years [10]. The absolute improvements in 10-year survival were 10.9% in node-positive and 5.6% in node-negative breast cancer. In contrast, women with ER-negative disease had little, if any, benefit [11,12]. Best results appear to be achieved after 5 years of treatment; thereafter, the beneficial effects decrease and toxicity increases [13–15], although the optimal duration of administration is still under investigation [3]. Nevertheless, tamoxifen-stimulated breast cancer is well recognized [16] and provides the rationale for stopping tamoxifen therapy at 5 years.

About half of the women with advanced ER-positive breast cancer will have a response to tamoxifen therapy, whereas only 5% with ER-negative breast cancer will have a response [4,14]. The reduction in the risk of contralateral breast cancer in adjuvant trials of tamoxifen led to its inclusion in randomized primary-prevention trials. Among the 13,388 participants in the breast cancer prevention trial, there was a 49% reduction in the risk of invasive breast cancer, but the benefit of tamoxifen was limited to ER-positive tumors with a 69% reduction [5].

Tamoxifen was also reported to reduce the risk of fractures, though not significantly. However, it was associated with increased risks of endometrial cancer, stroke, pulmonary embolism, deep vein thrombosis, and cataract, primarily in women 50 years of age or older [5,17–19]. Tamoxifen increased the risk of stroke (RR, 1.75; 95% CI, 0.98–3.20), deep vein thrombosis (RR, 1.71; 95% CI, 0.85–3.58), and pulmonary emboli (RR, 3.19; 95% CI, 1.12–11.15), although only the risk

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of pulmonary embolism reached statistical significance [5]. The incidence of pulmonary embolism was increased from 0.31 per 1,000 women per year to 1 per 1,000 women per year. The incidence of endometrial carcinoma was increased fourfold, but no deaths due to endometrial carcinoma occurred in the tamoxifen arm. Endometrial cancer occurred in 3.05 per 1,000 women per year taking tamoxifen [5]. Bernstein et al examined the effect of the known risk factors for endometrial carcinoma (i.e. obesity and previous estrogen use) in women taking tamoxifen [20]. They found no increase in endometrial cancer with tamoxifen use in the absence of these factors. Tamoxifen was also noted to increase the risk of cataract surgery from 3 per 1,000 to 4.72 per 1,000 per year [5].

No trial has shown improved survival with tamoxifen. In fact, there were slightly more deaths in the tamoxifen group of the IBIS-I trial due to an increase in thromboembolic events [9]. A recent evidence-based technology assessment by the American Society of Clinical Oncology indicated that tamoxifen's favorable effect on the risk of breast cancer must be weighed against its potential side effects in individual women [8]. The conclusions drawn from the assessment were: (1) for women with a 5-year projected breast cancer risk greater than 1.66%, tamoxifen (20 mg/day for 5 years) may be offered to reduce risk; (2) consideration of tamoxifen is appropriate for the goal of lowering the short-term risk of developing breast cancer; (3) risk/benefit models suggest that the greatest clinical benefit with least side effects are derived from use of tamoxifen in younger, premenopausal women who are less likely to have thromboembolic sequelae and uterine cancer, in women without a uterus, and in women at higher breast cancer risk; and (4) data do not as yet suggest that tamoxifen provides an overall health benefit or increases survival [8].

Therefore, the use of selective estrogen receptor modulators other than tamoxifen, such as the new-generation aromatase inhibitors or pure estrogen receptor antagonists, may be a better choice for breast cancer prevention. Results from the Study of Tamoxifen and Raloxifene (STAR) trial involving 20,000 women were released in April 2006, more than a year ahead of schedule [21]. The findings revealed that raloxifene's greatest advantage over tamoxifen appears to be fewer serious side effects, including uterine cancer, blood clots, and cataracts [21]. The results of this trial have prompted the manufacturer of raloxifene, Eli Lilly, to petition the Food and Drug Administration for permission to market raloxifene for breast cancer prevention. Physicians across the United States are now anticipating an influx of requests from postmenopausal women

for raloxifene [17]. Vastag further pointed out the vision of raloxifene, suggesting that raloxifene prevails in the STAR trial and may face an easier road to acceptance than previous drugs [17]. Only time will tell whether raloxifene will be the preferred choice.

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