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## *Perspectives and Commentaries*

# Review: Adjuvant Hormonotherapy for Breast Cancer

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ADEQUATE local therapy is available for primary breast cancer in the form of surgery ± radiotherapy. Unfortunately, the majority of women with breast cancer are destined to have disease recurrence and ultimately die of their disease. The interest in adjuvant therapy for selected patients with primary breast cancer has been kindled by improvements in systemic therapy for advanced breast cancer and by increased appreciation for the biology of treatment of minimal residual disease following primary therapy.

The use of hormones as adjuvant therapy in the primary treatment of breast cancer is not a new concept. The roles of radiation-induced menopause and surgical castration as adjuvants to primary therapy were explored over the last three decades. Various non-controlled studies and randomized controlled trials have yielded conflicting results; although several studies reported an effect of radiation-induced castration in delaying the appearance of distant metastases in both pre- and postmenopausal patients, the overall survival has not been improved statistically with either surgical oophorectomy or radiation to the ovaries.

Meakin *et al.* prospectively randomized premenopausal patients over the age of 45 and postmenopausal women following surgery and radiotherapy to the chest wall and regional lymph nodes to observation only, ovarian irradiation and ovarian irradiation plus prednisone (7.5 mg po q day for up to 5 yr) [1]. The combination of ovarian radiation plus small doses of continuous prednisone produced a significant delay in recurrence and prolongation in survival in this subset of premenopausal patients. No difference in time to recurrence nor in survival was detected in postmenopausal patients among the three arms. The beneficial effect of ovarian irradiation plus continuous prednisone in the premenopausal patients over the age of 45 did not become statistically significant until after 3 yr of follow up. It is important to note that the trial size was small and the duration of patient accrual was long.

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The data from the Princess Margaret Hospital study provided the best evidence that adjuvant hormonal therapy could improve survival in a selected subset of patients with breast cancer. The emergence of tamoxifen as an effective endocrine agent in the treatment of metastatic breast cancer coupled with its lack of serious side effects encouraged the development of adjuvant hormonal therapy trials with tamoxifen. Several large prospective randomized trials comparing adjuvant tamoxifen with placebo or no further therapy control arms following surgery ± radiotherapy have been initiated in the last decade.

In reviewing the results of four of the largest adjuvant tamoxifen trials, a number of issues must be kept in mind (Table 1). Does adjuvant therapy with tamoxifen improve survival or only delay recurrences? Are there specific subsets of patients who are most likely to benefit from adjuvant tamoxifen? Specifically, what is the effect of adjuvant tamoxifen therapy on disease-free survival and overall survival when analyzed according to menopausal status, axillary node status, and estrogen/progesterone receptor status? What is the optimal dose and duration of adjuvant tamoxifen? Do these trials address the impact of adjuvant tamoxifen on overall survival? A major difficulty in adjuvant trials for breast cancer is that relapses may occur many years following primary therapy; prolonged remissions may be obtained in patients with hormone therapy or chemotherapy. Overall survival is not only influenced by the initial adjuvant therapy, but also by subsequent salvage therapy used at the time of relapse. The secondary treatment following adjuvant relapse has not been controlled in most studies. Is disease-free survival, therefore, a valid endpoint for assessing the impact of adjuvant hormonal therapy in breast cancer?

In the first analyzed multicenter randomized trial from Copenhagen, the recurrence rates in premenopausal patients (after a median of a 36-month follow up) in the tamoxifen arm were lower than the placebo arm (21 vs. 35%, respectively), but the advangage did not reach statistical significance [2]. In the postmenopausal

*Table* 1.

| Trial | Surgery | ER | Groups (n. patients evaluable) | Adjuvant therapy | Disease-free survival | | | *Comments* |
|---|---|---|---|---|---|---|---|---|
| I. Copenhagen [2] 1974–1977 | Simple mastectomy ± LN dissection + postoperative radiotherapy | 66% had ER determinations | Premenopausal (202) | Tamoxifen 10 mg po t.i.d. × 2 yr | @ 36 mos | 79% | | In postmenopausal pts, ER+ pts had lower rate of recurrence than ER− pts regardless of treatment. |
| | | | | vs. | | | N.S. | |
| | | | | Placebo − yr | | 65% | | |
| | | | Postmenopausal (128) | Tamoxifen 10 mg po t.i.d. × 2 yr | | 76% | | |
| | | | | vs. | | 82% | p=0.004 | |
| | | | | DES 1 mg po t.i.d. × 2 yr | | | | |
| | | | | vs. | | 64% | | |
| | | | | Placebo × 2 yr | | | | |
| II. Danish Breast Cancer Group [3, 4] 1977–1982 | Total mastectomy with partial axillary dissection + postoperative radiotherapy | 14% had ER determinations | Postmenopausal $T_3$, $T_4$ and/or node positive (1650) | Tamoxifen 10 mg po t.i.d. × 48 wk | @ 36 mos, age 50–59 | 80% | | Recurrence rate in ER− pts exceeded that of ER+ pts by a factor of 2 regardless of treatment. |
| | | | | vs. | | | p=0.025 | |
| | | | | Placebo × 48 wk | | 60% | | |
| | | | | | @ 36 mos ≥4 positive lymph nodes | 62% | p=0.009 | |
| | | | | | | 38% | | |
| | | | | | @ 42 months, ER ≥100 fmol/mg cytosol protein | 70% | p=0.01 | |
| | | | | | | 52% | | |

*Table* 1 *continued*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| III. NATO [5, 6] 1977–1981 | Total mastectomy ± axillary node clearance + postoperative radiotherapy | 45% had ER determinations | Premenopausal (128) Postmenopausal (1157) | Tamoxifen 10 mg po b.i.d. × 2 yr vs. Observation | @ 45 mos, all patients | 73% 61% | p=<0.001 | 34% fewer deaths observed in the tamoxifen group. ER status did not predict effect of tamoxifen on treatment. |
| IV. Christie Hospital [7, 8] 1976–1982 | Simple or radical mastectomy ± axillary node sampling/total axillary node dissection. | Unknown | Premenopausal (373) | Ovarian irradiation (1500 rad in 4 fractions to pts <age 40; 500 rad in 1 fraction to pts >age 40) vs. Tamoxifen 10 mg po b.i.d. × 1 yr | No difference in overall survival | | | Comparing *all* pts according to subsets of axillary node positive, negative or unknown, patients in the tamoxifen group had a decrease in recurrence rate compared to radiation castration/observation groups ($P$=0.04). |
| | Postoperative radiotherapy to stage III and/or node positive patients | | Postmenopausal (588) | Tamoxifen 10 mg po b.i.d. × 1 yr vs. Observation | No difference in overall survival | | | |

patients, the rates of recurrence after a 36-month median follow up were lower in the tamoxifen and DES-treated group (24 and 18%, respectively) compared to the placebo group (36%).The relapse-free survival for tamoxifen and DES was statistically superior to placebo ($P = 0.004$). Forty-two per cent of the DES-treated group required discontinuation of therapy, however, because of adverse side effects. Tamoxifen was tolerated much better, with treatment discontinuation in 13%. Although the effect of nodal involvement on additive hormonal therapy cannot be determined from this study, tamoxifen and DES appeared to be superior to placebo for prevention of early recurrence in postmenopausal patients.

In the Danish Breast Cancer Group (DBCG), the rate of recurrence was significantly decreased in the adjuvant tamoxifen group in the subset 50–59 years of age (20% recurrence rate at 36-month median follow up vs. 40% recurrence rate in control arm, $P = 0.025$), and in the subset with four or more involved axillary lymph nodes (38 vs. 62% recurrent rate in control arm at 36-month median follow up, $P = 0.009$) [3].

An update from the DBCG in January 1985 analyzed the benefit of adjuvant tamoxifen after a median follow up of 42 months according to estrogen receptor status. Adjuvant tamoxifen resulted in an improved recurrence-free survival (70%) compared to control (52%, $P = 0.01$) at 48 months in the subset with estrogen receptor value $\geq$100 fmol/mg cytosol protein [4].

In the third trial, the Nolvadex Adjuvant Trial Organization (NATO), the preliminary analysis with median follow up of 21 months detected a significant difference in the percentage of patients relapse-free in the tamoxifen group (85.8%) vs. the observation group (79.5%, $P = 0.01$) with an estimated prolongation of the disease-free interval by 9 months [5]. An analysis according to menopausal status indicated that the improvement in the per cent disease-free at 21 months held for both pre- and postmenopausal patients, although the benefit was more striking in the postmenopausal group (75% disease-free on tamoxifen vs. 59.8% on observation).

The NATO presented an update in April 1985 after a median follow up time of 45 months [6]. Seventy-three per cent of the tamoxifen group vs. 61% of the observation group remained disease-free ($P<0.001$). Tamoxifen appeared to prevent both local/regional and distant disease, and 45 fewer deaths (34%) were observed in the tamoxifen group. Only 45% of patients had their ER status determined; the NATO concluded, however, that although ER status was of prognostic significance in relation to survival, it did not appear to predict the effect of tamoxifen treatment on survival.

The fourth trial from the Christie Hospital and Holt Radium Institute is reported in this journal with a 7-yr follow up on 1005 women who were entered onto their adjuvant tamoxifen trial [7, 8]. There was no difference in survival in the premenopausal group between tamoxifen vs. radiation menopause, and no difference in survival was noted for postmenopausal patients treated with tamoxifen vs. control. All patients were then analyzed according to whether the axillary nodes were negative, positive or node status unknown, and then comparison was made within the subgroups between tamoxifen vs. radiation menopause/control. There was an overall survival benefit for tamoxifen with 108 observed deaths in the tamoxifen group vs. 133 deaths in the irradiation menopause/control group ($P = 0.05$). Patients treated with tamoxifen had fewer events (defined as first evidence of relapse) than the control group (148 vs. 173, respectively, $P = 0.04$), and tamoxifen appeared to decrease the number of patients with distant metastases in post menopausal women compared to control (81 vs. 107, respectively, $P = 0.06$).

The observations from these large adjuvant trials suggest that tamoxifen benefits women by a delay in the time to relapse. Overall survival is not routinely shown to improve. The limitations of these studies are several and include the lack of a uniform definition of a premenopausal vs. postmenopausal patient, the impact of treatment according to number of involved axillary nodes is not uniformly available, and estrogen receptor and progesterone receptor status is available in only a minority of patients. Thus far the median follow up time is less than 48 months; continued follow up will be essential to detect any increase in disease recurrence or accelerated mortality associated with cessation of tamoxifen. The studies are comprised of relatively small numbers of patients, and consequently the detection of small differences in relapse-free survival and overall survival may be difficult. Although tamoxifen was well tolerated with minimal toxicity, prolonged follow up will be needed to determine the possible long-term adverse effects of tamoxifen.

To overcome some of these insufficiencies, R. Peto has analyzed data from all of the adjuvant trials looking at an overview of mortality by allocated treatment from available trials. He concludes that short-term survival differences can be demonstrated by this mass analysis for postmenopausal women treated with tamoxifen [11]. Peto's technique maximizes the survival difference through analysis of very large numbers of patients; the improved survival was in fact only a small benefit, with the reduction in short-term mortality only a few percentage points. The analysis by Peto

clearly indicates the limitations of conducting too many small studies. Since a high degree of statistical significance was suggested by a preliminary overview of trials, many questions have been raised. Further analyses are planned in the fall of 1985.

What are possible future directions for adjuvant hormonal clinical trials? The dimethylbenzanthracene (DMBA)-induced and *N*-nitrosomethylurea (NMU)-induced rat mammary carcinoma model has been used to study the control of hormone-dependent cancer. In these laboratory models, short-term tamoxifen (30-day course) caused a delay in tumor appearance and only a slight decrease in the cumulative number of tumors that were induced by 200 days. In contrast, continuous tamoxifen (170 days) maintained the majority of the animals in a tumor-free state [9]. These data suggest that tamoxifen in an adjuvant setting may act as a suppressant, placing cells in the $G_1$ and $G_0$ phase of the cell cycle, rather than acting as a tumoricidal agent. Modest benefits have been obtained thus far with adjuvant 'short-term' (1–2 yr) tamoxifen. The clinical implication of the laboratory models is that long-term tamoxifen (≥5 yr) may be optimal to maintain suppression of recurrent breast cancer.

A pilot adjuvant study at the Wisconsin Clinical Cancer Center tested the use of long-term tamoxifen (at least 5 yr) following 1 year of combination chemotherapy [10]. Tamoxifen was well tolerated. In addition, serum levels of tamoxifen and its metabolites remained relatively constant throughout the study period, indicating the lack of induced drug metabolism and tolerance to tamoxifen.

Future trials will need to address the use of long-term tamoxifen through large randomized studies compared to surgery alone. The value of adding tamoxifen to cytotoxic therapy (concurrently and/or after cytotoxic therapy is completed) also remains unproven. Whether tamoxifen benefits all women regardless of menopausal or ER and PgR status also needs to be determined. Very large numbers of patients (≥10,000 per arm) may be needed with long-term follow up before definitive answers on improved survival become available. Attention needs to be placed on controlling the secondary therapies as well. Such an undertaking will require cooperation among a variety of cooperative groups both in the United States and Europe.

## REFERENCES


1. Meakin JW, Allt WEC, Beale FA *et al.* Ovarian irradiation and prednisone following surgery and radiotherapy for carcinoma of the breast. *Eur J Cancer* 1980 (supplement), **2**, 179–181.
2. Palshof T, Mouridsen HT, Daehnfeldt JL. Adjuvant endocrine therapy of primary operable breast cancer. Report on the Copenhagen Breast Cancer Trials. *Eur J Cancer* 1980 (supplement), **2**,183.
3. Rose C, Thorpe SM, Mouridsen HT *et al.* Antiestrogen treatment of postmenopausal women with primary high risk breast cancer. *Breast Cancer Res Treat* 1983, **3**,77.
4. Rose C, Thorpe SM, Anderson KW *et al.* Beneficial effect of adjuvant tamoxifen therapy in primary breast cancer patients with high estrogen receptor values. *Lancet* 1985, **1**,16.
5. Nolvadex adjuvant trial organization controlled trial of tamoxifen asadjuvant agent in management of early breast cancer. *Lancet* 1983, **1**,257.
6. Controlled trial of tamoxifen as single adjuvant agent in management of early breast cancer — analysis at six years by Nolvadex adjuvant trial organization. *Lancet* 1985, **1**,836.
7. Ribeiro G, Palmer MK. Adjuvant tamoxifen for operable carcinoma of the breast: report of clinical trial by the Christie Hospital and Holt Radium Institute. *Brit Med J* 1983, **286**, 827.
8. Ribeiro G and Swindell R. The Christie Hospital tamoxifen (Nolvadex) adjuvant trial for operable breast cancer—7 year results. *Eur J Cancer Clin Oncol* 1985, **21**,879–900.
9. Jordan VC. Laboratory studies to develop general principles for the adjuvant treatment of breast cancer with antiestrogens: Problems and potential for future clinical applications. *Breast Cancer Res Treat* 1983, **3** (supplement 1), 73.
10. Tormey DC and Jordan VC. Long-term tamoxifen adjuvant therapy in node-positive breast cancer: a metabolic and pilot clinical study. *Breast Cancer Res Treat* 1984, **4**, 297.
11. Editorial. Review of mortality results in randomised trials in early breast cancer. *Lancet* 1984, **2**, 1205.