Pergamon

European Journal of Cancer Vol. 32A, No. 12, pp. 2173–2176, 1996

Printed in Great Britain
0959-8049/96 $15.00 + 0.00

PII: S0959-8049(96)00227-4

Short Communication

Possible Deleterious Effect of Tamoxifen in Premenopausal Women with Locoregional Recurrence of Breast Cancer

M.M. Borner,[1] M. Bacchi[2] and M. Castiglione[1,2]

[1]Institute of Medical Oncology, Inselspital, CH-3010, Bern, Switzerland; and [2]Swiss Group for Clinical Cancer Research, Coordinating Center, Bern, Switzerland

Tamoxifen (TAM) treatment following isolated locoregional recurrence of breast cancer significantly increases 5-year disease-free survival rates compared with observation alone in potentially hormone-responsive patients [*J Clin Oncol* 1994, 12, 2071–2077]. The treatment outcome was re-analysed by menopausal status (stratification factor) in 35 premenopausal and in 132 postmenopausal patients. Disease progression was highly reduced by tamoxifen in the postmenopausal group and was similar to control in the premenopausal group. However, the 5-year cumulative incidence analysis of the type of first failure showed TAM to be associated with increased incidence of distant metastases ($P = 0.01$) in premenopausal patients. TAM reduced local progression ($P = 0.40$) in premenopausal and both types of failure ($P = 0.16$ and $P = 0.001$, respectively) in postmenopausal patients. Administration of TAM was associated with a decrease of 5-year overall survival from $90 \pm 7\%$ to $60 \pm 14\%$ in premenopausal patients. Although cautious interpretation of these results is highly recommended due to the small patient numbers and the retrospective subset analyses, these findings might be worthy of further investigation in larger trials. Prospective randomised studies to test hormonal treatment outcome by menopausal status should be encouraged in breast cancer.

Key words: breast cancer, tamoxifen, hormonal treatment, locoregional recurrence, metastases, menopausal status

Eur J Cancer, Vol. 32A, No. 12, pp. 2173–2176, 1996

INTRODUCTION

THE USE of tamoxifen has substantially improved the natural history of postmenopausal women with breast cancer [1]. However, the benefits of adjuvant tamoxifen are less pronounced in premenopausal women [1, 2] and clinical experience with tamoxifen in premenopausal metastatic disease is limited [3]. It has been recently reported that tamoxifen may increase the incidence of contralateral breast cancer in premenopausal women [4], and that the tamoxifen-associated risk of developing endometrial cancer may also be dependent on menopausal status [5].

Isolated first locoregional recurrence affects 3 to 27% of women after mastectomy for breast cancer [6]. We recently published the results of the only randomised clinical trial thus far assessing the effect of tamoxifen in this setting [7]. 167 women with potentially hormone-responsive (oestrogen receptor (ER) positive or unknown) locoregional recurrence were randomised to tamoxifen or observation after excision and radiotherapy of the recurrence. We found a highly significant (log rank $P = 0.007$) reduction in disease progression with the use of tamoxifen compared with the control. This was mainly due to the reduction of further local recurrences. Overall survival has not yet been affected (log rank $P = 0.77$) after 6.4 years of median follow-up. Patients were prospectively stratified for menopausal status in this study and an interesting question is whether menopausal status has an impact on treatment outcome in locoregionally recurrent breast cancer. We report here on the unexpected effect of tamoxifen in this well controlled patient group.

Correspondence to M.M. Borner.
Received 14 Feb. 1996; revised 8 May 1996; accepted 11 Jun. 1996.

Table 1. Selected characteristics and survival figures of the study population by menopausal status and treatment assignment

	Premenopausal		Postmenopausal	
	Control ($n = 20$)	TAM ($n = 15$)	Control ($n = 61$)	TAM ($n = 71$)
Median age (years)	43	41	59	60
Nodal status at diagnosis of primary (%)				
Positive	40	40	46	49
Negative	60	60	54	51
Oestrogen receptor status (%)				
Positive	60	53	66	72
Unknown	40	47	34	28
Previous adjuvant chemotherapy (%)				
Yes	45	47	38	44
No	55	53	62	56
5-year overall survival (% ± S.D.)	90 ± 7	60 ± 14	71 ± 7	78 ± 6
5 year disease-free survival (% ± S.D.)	55 ± 12	57 ± 14	29 ± 7	60 ± 7

PATIENTS AND METHODS

The study design has been described elsewhere [7]. In brief, the study population consisted of 167 'good risk' women with locoregional recurrence of breast cancer. Locoregional recurrence was defined as first reappearance of cancer in the ipsilateral (side of primary tumour) chest wall, shoulder, neck, and upper arm or the axillary, infraclavicular, supraclavicular, and cervical lymph nodes on either side. 'Good risk' was defined as ER positivity of the recurrence or, in case of unknown ER receptor status, disease-free interval (DFI) of more than 12 months and less than 4 recurrence nodules with a maximal diameter of 3 cm. Premenopausal status was defined as occurrence of the last menstruation within one year from study entry or, in case of a previous hysterectomy patient age of less than 52 years. ER/PR levels of $\geqslant 10$ fmol/mg cytosol protein using standard methods were considered positive. The local treatment consisted of radical excision of the recurrence followed by local radiotherapy. A total dose of 5000 cGy was given to the involved region at 200 cGy per fraction 5 days a week. After local treatment, patients were stratified according to menopausal status, adjuvant chemotherapy and axillary node involvement of the primary tumour and centrally (SAKK Koordinationszentrum, Bern, Switzerland) randomised by telephone to either observation alone or to systemic treatment (tamoxifen 20 mg per day orally) until disease progression. Patients pretreated with adjuvant tamoxifen were not eligible for this study.

The Kaplan–Meier method was used to estimate distributions of disease-free survival (DFS) and overall survival (OS) [8]. Differences in time distributions were evaluated by the log rank test [9]. A multivariate analysis using the Cox proportional-hazards model was performed [10]. The interaction between treatment and menopausal status was tested as suggested by Simon [11]. Cumulative incidence functions totalling the overall event probability were estimated for the competing events and compared between the treatment arms [12, 13]. All P values were derived from a two-sided test for significance.

RESULTS

35 premenopausal and 132 postmenopausal patients entered this study. Treatment and menopausal groups were balanced for possible confounding variables such as nodal status at diagnosis and previous adjuvant chemotherapy (Table 1). A slight imbalance of tumours with positive or unknown ER receptor status was observed between TAM and control groups in premenopausal women. This difference was caused by 1 patient. Cancer-unrelated deaths were equally distributed.

The Kaplan–Meier distribution of DFS for both menopausal groups is plotted in Figure 1a. Further disease progression was highly reduced by tamoxifen in the postmenopausal group and was similar to control in the premenopausal group. The failure sites were examined in detail. The 5-year cumulative incidence analysis of the type of first failure [14] showed that tamoxifen was associated with increased incidence of distant metastases from 10 to 29% ($P = 0.01$) in premenopausal women, while local progression was reduced from 30 to 14% ($P = 0.40$). In postmenopausal women, the incidence of relapse at both progression sites was decreased by tamoxifen (local relapse from 27 to 9% [$P = < 0.001$]; distant metastases from 30 to 24% [$P = 0.16$]).

Figure 1b shows that tamoxifen was associated with decreased survival in premenopausal patients, while having a prolonging effect on survival in postmenopausal patients. The premenopausal control group had the most favourable outcome with no fatal events after 2 years of follow-up. The corresponding 5-year survival figures are shown in Table 1. In view of this differential effectiveness of tamoxifen depending on menopausal status, we decided to apply an interaction test [11] to have quantitative information of whether this difference was the result of chance fluctuation. The test for interaction between treatment arm and menopausal status was significant ($P = 0.05$) in the Cox model for overall survival.

DISCUSSION

Recent indirect evidence suggests that tamoxifen could have a differential effect on the growth of hormone sensitive cancer depending on the menopausal status of the affected women [4, 5]. Thus, we re-analysed our randomised study about the role of systemic treatment with tamoxifen after surgery and radiotherapy in isolated locoregional recurrence of breast cancer [7]. We found that tamoxifen seemed to be associated with an increased risk for metastatic progression in premenopausal women, while it reduced local and distant failure in postmenopausal women. As a consequence, the 5-year overall survival figures were highest for the premeno-

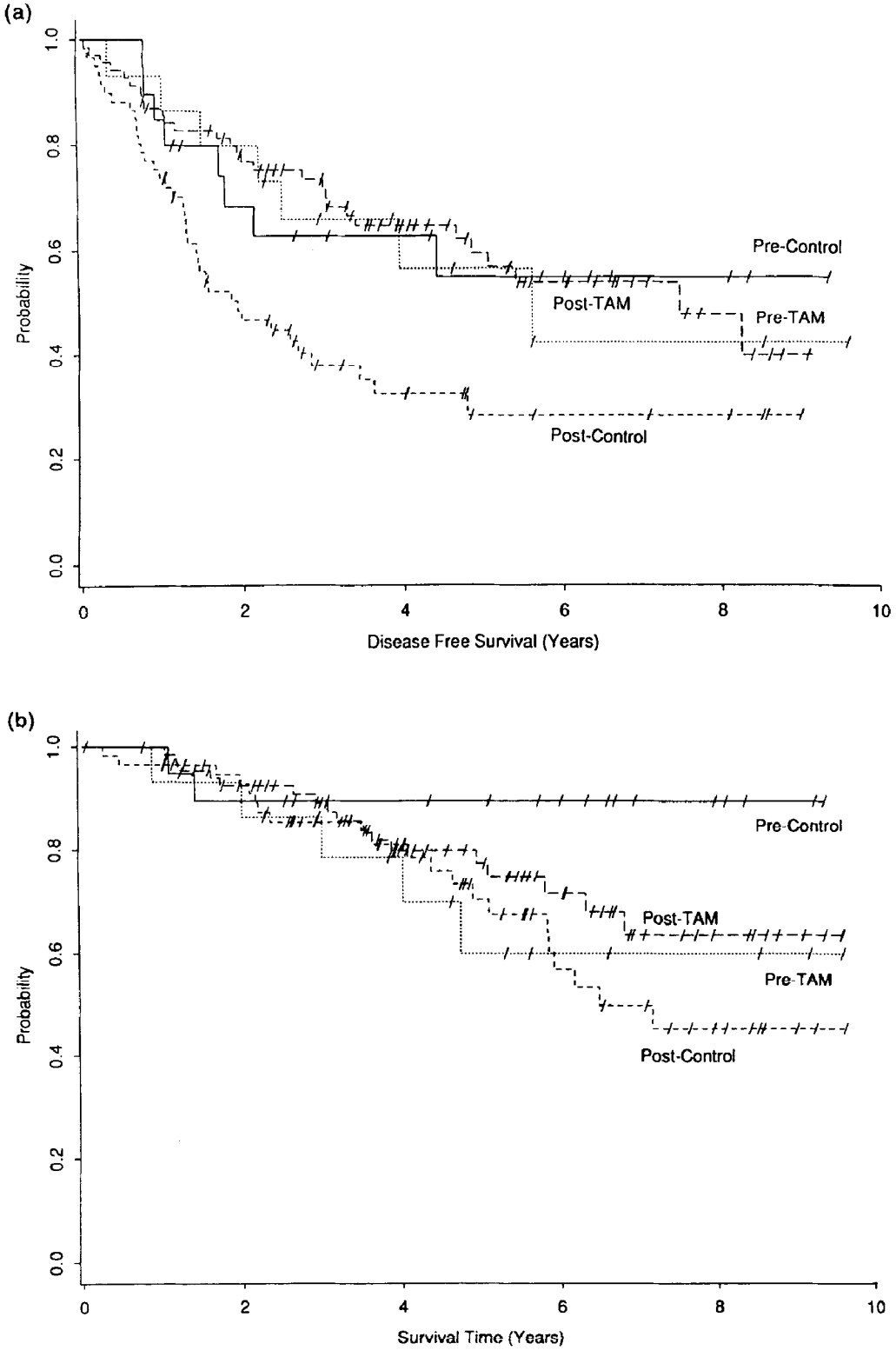

Figure 1. Disease-free survival (a) and overall survival (b) of the study population according to treatment group (TAM; Control) and menopausal status (Pre; Post).

pausal control group where no fatal events have been observed after 2 years. The test of interaction between treatment arm and menopausal status was significant ($P = 0.05$) in the Cox model for overall survival thus increasing the probability, that these results were not only due to chance fluctuation.

Since tamoxifen is a widely used drug in general practice, the detection of a deleterious effect on a subgroup of preme-

nopausal women is of potential importance. Therefore, it is crucial to discuss potential pitfalls of this analysis. Given the small numbers of patients, the results should not be overinterpreted. Although the study was prospectively stratified by menopausal status and the subgroups seemed balanced for possible confounding variables, even the slightest imbalances can have a major impact. Furthermore, our findings are the result of a subset analysis which was not intended at the initial study planning. These data should be used for hypothesis generation and should be confirmed in larger studies [15].

Interestingly, the 5-year overall survival of postmenopausal patients in our study was shorter compared with premenopausal patients. This contrasts with findings in the literature which show young patient age to be an independent risk factor for local recurrence as well as for distant metastases after mastectomy [16]. We speculate that patients with isolated locoregional recurrence of breast cancer represent a favourable subgroup of premenopausal breast cancer patients. First relapse as locoregional failure without manifest distant metastases might be the expression of a less aggressive biological behaviour of the carcinoma.

A detrimental effect of adjuvant tamoxifen in premenopausal women (patients $\leqslant 50$ years of age) was not seen in large randomised trials [2, 17]. An exception is study B-09 by the National Surgical Adjuvant Breast and Bowel Project, where the addition of tamoxifen to L-phenylalanine mustard plus 5-fluorouracil negatively affected survival [18]. However, this result does not necessarily imply a direct negative effect of tamoxifen, but could rather be taken as evidence for an interaction between this chemotherapy regimen and tamoxifen. A possible biological explanation for our findings is that isolated locoregional recurrence might not reflect the adjuvant situation after resection of the primary, but represents first manifestation of metastatic breast cancer. It is conceivable that, in this situation, micrometastases at other sites have already restarted proliferation, gradually losing sensitivity to the cytotoxic action of tamoxifen. It might even be considered that tamoxifen has a tumour growth stimulating effect in premenopausal women by elevating circulating oestrogen [3]. Our data provide further evidence that local and distant metastases show different biological behaviour. Genetic alterations, which allow a metastatic cancer cell to survive in distant sites can also be expected to render it more independent of hormonal stimulation. This might explain the preferential effect of tamoxifen on locoregional failure [7].

Although the small patient numbers and the subset analyses preclude definitive statistical evaluations, these results emphasise the need to consider menopausal status when administering agents with hormonal activity. Therefore, we would like to encourage the design of prospective randomised studies to test the impact of menopausal status on hormonal treatment outcome in primary and metastatic breast cancer.

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Acknowledgements—We would like to thank A. Goldhirsch, R. Gelber and J. Cuzick for their helpful suggestions.