Eur J Cancer, Vol. 27, No. 6, p. 806, 1991.
Printed in Great Britain
0277-5379/91 $3.00 + 0.00

Development of Breast Cancer during Long-term Tamoxifen Therapy for Lymphangioleiomyomatosis

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TAMOXIFEN BLOCKS the effects of oestrogen on the breast, but does not act as a pure antioestrogen [1] and is an effective palliative therapy for a proportion of women with advanced breast cancer. In addition tamoxifen can improve survival in certain subgroups of women when used as adjuvant treatment following initial surgery [2]. These data combined with its low incidence of side-effects has lead to proposals in the UK and the USA to investigate its use as a primary prevention in women judged to be at risk of developing breast cancer [3, 4] and pilot studies have commenced [5]. However, as tamoxifen is usually given to women with established breast cancer, there is no information on the development of breast cancer in women given it for other reasons. We have recently observed such a case.

A 49-year-old woman was investigated in January 1988 for pulmonary fibrosis with recurrent pneumothoraces and pleural effusions and was found to have pulmonary lymphangioleiomyomatosis following open lung biopsy. Because of anecdotal reports of tamoxifen use in this rare condition [6] she was given tamoxifen 20 mg each day continuously and over the next 2 years her chest X-ray and pulmonary function assessments remained stable and she symptomatically improved and suffered no further pneumothoraces. In December 1989 she was found to have a 2 cm left breast carcinoma, predominantly intraduct carcinoma but with foci of microinvasion. The intraduct component extended to the deep resection margin of the lumpectomy but the patient refused to proceed to mastectomy and the axillary nodes were not sampled and hormone receptor status was unknown. Local radiotherapy was thought inadvisable because of the risk of worsening the underlying pulmonary fibrosis. Over the ensuing 12 months there has been no evidence of recurrence and mammography of the contralateral breast is normal. The tamoxifen has been continued and the lymphangioleiomyomatosis remains stable. The patient had a hysterectomy many years previously but had no menopausal symptoms and serum leutinising hormone and follicle stimulating hormone levels are in the premenopausal range. She has no family history of breast cancer.

The growth rates of primary breast cancers are highly variable. In a study using serial mammography the mean tumour doubling time was 325 days but varied from too rapid to be measured to no apparent growth [7]. As 20–30 doublings are normally required to produce a clinically evident tumour, in our patient the initial malignant event probably occurred at a considerable time prior to the commencement of tamoxifen. However, the administration of tamoxifen did not prevent the progression to clinically overt breast cancer.

This case illustrates that breast cancer can develop during continuous tamoxifen given for illnesses other than breast cancer. This, however, should not deter the important studies [5] in progress which attempt to determine if tamoxifen can reduce the risk of breast cancer among healthy women with a family history of breast cancer. The use of family history as a selection criterion for preventative tamoxifen therapy in healthy women has been questioned [1], but the lack of this factor in our patient who developed breast cancer despite continuous tamoxifen tends to support the restriction of this prophylactic therapy to healthy women with a close family history of breast cancer.

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Received 28 Feb. 1991; accepted 6 Mar. 1991.

Eur J Cancer, Vol. 27, No. 6, pp. 806–807, 1991.
Printed in Great Britain
0277-5379/91 $3.00 + 0.00

Combined Goserelin and Tamoxifen in Premenopausal Advanced Breast Cancer: Duration of Response and Survival

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THE ENDOCRINE effects and efficacy of the luteinising hormone releasing hormone (LH-RH) agonist goserelin as initial hormone therapy for premenopausal advanced breast cancer patients have been reported [1–3]. In an early study [2] of 53 patients we reported a response rate of 31%, comparable to our experience with surgical ooporectomy [4]. Whilst LH-RH agonists reduce ovarian activity they do not interfere with peripheral oestradiol production, a factor believed to play a role in promoting hormone

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sensitive breast cancer growth in postmenopausal women; these effects may be inhibited by tamoxifen. Such a combination induces a more effective suppression of follicle stimulating hormone (FSH) and oestradiol [5]. We report our clinical experience of the combination with particular address to the duration of response and survival.

50 premenopausal patients, median age 42 (range 25–51) have received depot goserelin (3.6 mg) in combination with tamoxifen (20 mg twice a day). Disease sites included stage III tumours (11), locoregional recurrence (3) and metastases (36). The major sites of metastatic disease were bone (12), pulmonary (8), bone/pulmonary (8) and visceral (8).

Tumour steroid hormone receptor status was known in 38 patients and was considered positive when a value > 15 fmol/mg cytosol protein was obtained [6] (Abbott ER-EIA, monoclonal). Patients were assessed for response according to UICC criteria [7]. The British Breast Group's recommendation [8] that the minimum duration of remission be 6 months was also adhered to. Actuarial survival analysis was performed using the statistical computer package SPSSX-21 life table analysis [9], which calculates Gehan's generalised Wilcoxon test for censored data.

9 patients (18%) with UICC assessable disease [7] showed an objective response of at least 6 months duration. Complete responses (CR) were seen in 5 patients (10%), the duration of which was over 29 months; 2 had stage III disease and 3 metastases. Static disease (SD) occurred in 15 patients (30%). The remaining 26 patients had (52%) progressive disease (PD) within 6 months of starting therapy.

Whilst no patient with responsive disease (CR + PR) has yet progressed (median follow-up over 29 months), the median duration of response for SD was only 18 months ($P = 0.002$); there were no significant difference in survival (2 deaths in SD group only). The median survival of the PD group was 9 months. Primary tumour oestrogen receptor (ER) status was available in 38 patients (76%); 16 were ER positive and 22 ER negative. 7 of the 9 patients responding to goserelin and tamoxifen were ER positive; 2 had unknown receptor status. Of the 5 patients showing a complete response, 4 had ER positive primary tumours. 21 of 22 patients with ER negative tumours had progressive disease. Grouping together responsive and static disease, the oestrogen receptor status of the primary tumour correlates significantly with the prediction of response ($P = 0.01$, Fisher's exact test). Although the overall numbers are small, oestrogen receptor positivity appears to be associated with an improved survival ($P < 0.0001$, log rank analysis); see Fig. 1.

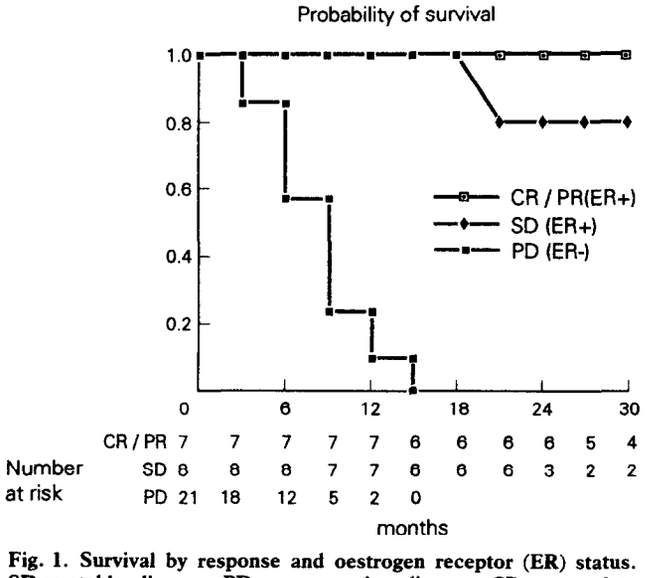

Fig. 1. Survival by response and oestrogen receptor (ER) status. SD = stable disease, PD = progressive disease, CR = complete response, PR = partial response.

Administration of the LH-RH agonist goserelin to premenopausal advanced breast cancer produces a rapid desensitisation of the pituitary gland to endogenous LH-RH with resultant falls in circulating LH and FSII [1–3]. Castrate levels of oestradiol and progesterone are produced within 3–4 weeks. This ability to reduce serum oestradiol is not influenced by either the patients age or weight. A theoretical limiting factor to treatment with LH-RH agonists as with radiation castration is their inability to immediately suppress ovarian activity; surgical oophorectomy produces castrate levels of oestradiol within 2–7 days [10].

Tamoxifen is widely used as initial therapy in postmenopausal patients with advanced breast cancer owing to its low toxicity and proven efficacy. Having made a patient postmenopausal with goserelin it would seem sensible to then add tamoxifen. In this retrospective study of 50 patients we report an objective response of only 18%, with a further 30% of patients showing static disease. There were no significant survival differences between these two response groups. The extended period of disease stabilisation may represent a developing response to tamoxifen mediated through the cytostatic effects of the antioestrogenic drug. It would appear that the presence of the oestrogen receptor in the primary tumour is predictive of a response to goserelin and tamoxifen. An international multicentre randomised trial comparing the clinical efficacy of goserelin and tamoxifen vs. goserelin alone as initial therapy, with tamoxifen being added on tumour progression, is near completion.

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