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THE ROLE OF ENDOCRINE THERAPY IN PRIMARY BREAST CANCER

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Summary—A recent overview of the results of all trials of adjuvant chemotherapy suggests a clinically and statistically significant advantage for premenopausal women with positive axillary nodes. The results of the same approach for all other women with early breast cancer are very disappointing. These data suggest that contrary to the original hypothetical model, adjuvant chemotherapy is exerting its effect indirectly via chemical castration. In contrast, the results of trials of adjuvant tamoxifen have been more promising and, again, in contrast to the original premises, it would appear that a modest improvement in survival and delay in recurrence can be achieved amongst all groups of women independent of age, nodal status and oestrogen receptor content of the primary tumour. In order to explain these counter-intuitive observations, it is necessary to elaborate an alternative biological model. This paper describes the current thinking on the mode of action of the "anti-oestrogens" and the possible role of inhibitory growth factors activated indirectly by anti-oestrogens. Future trials of adjuvant systemic therapy for early breast cancer should include studies on the duration of tamoxifen, comparing 2 yr with longer, and a comparison of tamoxifen alone with polychemotherapy for premenopausal node positive patients.

INTRODUCTION

The majority of patients with early breast cancer and positive axillary nodes die of cancer in spite of perfect loco-regional therapy. Therefore, they carry occult micro-metastases present at the time of diagnosis, and cure can only result from the addition of an effective systemic therapy. Experience with advanced breast cancer demonstrates an objective response-rate of the order of 60%, with prolonged combination therapy, which is twice that expected with an endocrine approach. *Ipso facto*, node positive patients should be cured by adjuvant systemic chemotherapy. However, a recent review of the results of randomized controlled trials of adjuvant chemotherapy has arrived at the following general conclusions [1]:

(a) Whatever combination regimen is used there is likely to be a significant delay in the time to first relapse.

(b) Although many individual trials have yet to show an improvement in crude survival, a statistical overview of all the available data suggests that a 30% reduction in the risk of dying over the first 5 yr may be achieved following the treatment of premenopausal women with node positive disease. The benefits for postmenopausal women are, to say the least, marginal.

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What, therefore, are the biological implications of these results? Firstly, there is little doubt that the natural history of early breast cancer has been perturbed. Whether this pertubation will translate itself into a useful therapeutic advantage for groups other than premenopausal node-positive patients remains to be seen. Secondly, the intriguing difference between the behaviour of pre- and postmenopausal women deserves some explanation. The chemotherapy lobby is not short of inductivists and much support has been generated for the concept that the effect of adjuvant systemic chemotherapy is dose-related [2]. Postmenopausal women seem incapable of tolerating the maximum ("optimum") doses prescribed. This suggestion requires further exploration, with trials of high-dose vs low-dose chemotherapy. Yet, at the same time, if older women were incapable of tolerating high-dose chemotherapy, then this surely is an inherent defect of the treatment unless one is prepared to push the drugs beyond the tolerance of the patient, surely a dangerous and inhumane policy. An alternative explanation for this differential effect might be that the cytotoxic drugs are mediating their effect by a chemical castration.

This hypothesis has already won support, following studies of ovarian and pituitary function in women receiving adjuvant chemotherapy [3]. It follows, therefore, that to test the hypothesis generated by the trials of adjuvant chemotherapy, one should conduct trials of adjuvant endocrine therapy

investigating prophylactic castration and the use of adjuvant tamoxifen.

TRIALS OF ADJUVANT ENDOCRINE THERAPY

Trials of prophylactic castration following local treatment for cancer are not new but have suffered in the past from inadequate sample size leaving uncertainty as to its potential benefit. This subject has recently been reviewed, suggesting that such an approach might indeed produce results of the same order achieved by poly-chemotherapy for premenopausal women but at the great expense of inducing a premature menopause in young women already facing up to the threat of loss of the breast [4]. For the purpose of this paper, though, I wish to concentrate on the trial of tamoxifen therapy, which can be judged to have had the most profound effect on our biological thinking about the disease. The Nolvadex Adjuvant Trial Organisation (NATO) launched a study in 1977 to investigate whether the anti-oestrogen tamoxifen (Nolvadex) would have any benefit for women undergoing mastectomy for early breast cancer [5]. Approximately 1300 patients were recruited over a period of $2\frac{1}{2}$ yr. These consisted of premenopausal node positive cases and postmenopausal node positive and negative cases. Following local therapy women were randomized to the group receiving tamoxifen, 10 mg twice daily for 2 yr, or to an untreated control group. A second-order hypothesis suggested that the women most likely to benefit were those whose primary tumour was rich in oestradiol receptor (ER) content. Therefore, as a parallel study, attempts were made to collect samples of the tumours from all patients entered into the trial. However, for logistic reasons, this was only possible in about 50% of the cases. The published data have demonstrated a significantly prolonged disease-free interval in the treated group as a whole, which has recently been translated into a 30% reduction in the risk of dying within the first 5 yr following treatment [6]. Support for the fact that this result was not a statistical fluke has emerged from the statistical overview conducted by Mr Richard Peto and his colleagues and presented at the Consensus Development Conference at the National Cancer Institute in Washington, U.S.A., in September 1985 [7]. Following this presentation, the NCI sanctioned the use of tamoxifen as monotherapy for the majority of women over the age of 50 at the time of diagnosis. Paradoxically, a Cox's multi-variant regression analysis within the NATO trial has failed to demonstrate any interaction between the treatment and subgroups divided according to menopausal, nodal or ER status [8].

BIOLOGICAL CONCLUSIONS FROM TRIALS OF ADJUVANT TAMOXIFEN

If the survival advantage of patients treated for 2 yr with tamoxifen persists long-term then this would suggest that the anti-oestrogen has a tumourocidal capacity for the putative micrometastases present at the time of the diagnosis. This in itself would be interesting, suggesting that subclinical tumour deposits are biologically different from overt metastatic disease. Of potentially greater interest is the suggestion that the oestrogen-receptor status of the primary tumour does not predict the likelihood of response to adjuvant tamoxifen. As such an outcome fails to reinforce popular prejudice there would naturally be the temptation to ignore or reject these data. It has already been suggested that the measurement of ER in a multicentre trial with inter- and intra-laboratory variation will produce many false negative results. This, indeed, may be the case, but it remains unquestionable that the assay of ER in this study has told us something of biological relevance about the primary cancers, as there is a powerful correlation between the ER status and prognosis, irrespective of primary or adjuvant therapy [8]. Rather than ignore these data out-of-hand, I believe it will be more fruitful to try to incorporate them within a modified hypothesis that can explain previous observations about the behaviour of breast cancer whilst at the same time incorporating the new and apparently irreconcilable observation. There is little doubt that the major pathway mediating the anti-tumour effect of tamoxifen in advanced breast cancer is via the oestradiol receptor; but the observations from the NATO trial raise the question as to whether tamoxifen exerts some of its effect on microscopic foci of the disease by another pathway. Recently, ubiquitous tamoxifen-binding protein has been discovered in tissues, which is unrelated to the ER [9]. Furthermore, tamoxifen in sufficiently high concentrations can inhibit the growth of both oestrogen-receptor positive and oestrogen-receptor negative human breast cancer cell lines [10]. Perhaps tamoxifen binding to this cytosolic protein or to other proteins like protein kinase C can interfere with another fundamental biochemical pathway upon which the continued growth of the cancer cell is dependent.

Exciting new discoveries concerning the nature of oncogenes and the relationship between oncogenic sequences in the cellular genome, and the production of specific growth factors or the expression of growth factor receptors, could easily be incorporated with these observations into a new biological model concerning the nature of breast cancer [11]. If tamoxifen can inhibit the cellular cascade of biochemical reactions which are a consequence of the activation of the epidermal growth factor receptor then this might suggest that the oestradiol receptor status of the breast cancer is merely an epiphenomenon of cellular differentiation, indirectly reflecting the rate of inappropriate growth factor activation. Thus, the ER serves as a prognostic indication, reflecting growth rate of the cancer rather than simply an expression of endocrine sensitivity. With this model, the oestrogen receptor could act as an amplifying mechanism concentrating

the anti-oestrogen within the cancer cell, where it can act as an anti-growth factor. This would then explain the apparent sensitivity of anti-oestrogen for advanced breast cancer amongst the oestrogen-receptor positive cells, whilst at the same time explaining why it retains modest activity against microscopic deposits of oestrogen-receptor negative cancer cells. Further support to the idea that the ER is an indirect expression of the rate of growth factor production comes from the following observations: ER positive cancers are predominantly well-differentiated on histological grading [12]. The ER status of breast cancers is inversely correlated with the rate of replication of cells *in vitro* [13]. Growth factors are known to potently attract monocytes [14] and a monocytosis is a recognized response to an actively growing tumour, and a heavy stromal round cell infiltrate is associated with a negative ER status [15]. Finally, two recent pieces of work have shown an inverse correlation between the oestrogen-receptor content of a breast cancer and the expression of epidermal growth factor receptors (EGFR) using specific monoclonal antibodies raised against EGFR [16, 17].

To summarize, therefore, at one extreme we might have a breast cancer with a very high rate of expression of EGFR, where the rate of replication and protein synthesis does not allow sufficient time or amino acids for the assembly of ER, whilst at the other extreme of EGFR expression, ER assembly precedes the completion. This then raises the intriguing possibility that anti-oestrogens may slow the tumour via an anti-growth factor pathway until ER is reassembled, and the cancer cell is redifferentiated, as a result of which the anti-oestrogen is further concentrated, exhibiting its secondary effect along the classical pathway.

All the predictions of this hypothesis are eminently testable, guaranteeing its refutation or elaboration with time. In the meantime, new trials are under way to investigate the optimum duration of adjuvant tamoxifen and its inter-relationships with the extent of loco-regional therapy and systemic chemotherapy.

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