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Perspectives and Commentaries

Combination Endocrine Therapy in Breast Cancer

BASIL A. STOLL
Oncology Department, St. Thomas' Hospital, London, U.K.

(A COMMENT ON: Alexieva Figusch JA, Blankenstein MA, de Jong FH, Lamberts SWJ. Endocrine effects of the combination of megestrol acetate and tamoxifen in the treatment of metastatic breast cancer. *Eur J Cancer Clin Oncol* 1984, **20**, 1135–1140.)

ALEXIEVA-FIGUSCH and her colleagues [1] report on the endocrine effects of combining an antioestrogen with a progestin in postmenopausal women with advanced breast cancer. To evaluate such strategies for improving, prolonging or restoring response in metastatic breast cancer we need to examine how far endocrine modalities are non-cross-resistant in this disease and also the results of trials using either concurrent or sequential combinations. We must consider whether it is possible to: (a) induce hormone sensitivity in resistant (ER–) clones of a tumour; (b) delay the development of hormonal autonomy in a tumour under treatment; or (c) restore hormonal sensitivity in a tumour when clinical response has been lost. The rationale of such an approach is examined in detail elsewhere [2].

CONCURRENT COMBINATION OF ENDOCRINE THERAPY

It is often suggested that endocrine modalities may be non-cross-resistant in their effect on the growth of breast cancer, because regression may occur following a second endocrine modality after loss or failure of response to the primary endocrine therapy. About 50% of tumours losing response to primary therapy will show response to secondary therapy, and in addition, about 20% of those which failed to respond to primary therapy will show response to secondary therapy [3]. There is a need also to explain reports that the oestrogen-tamoxifen sequence is more effective than the opposite order, and that the hypophysectomy-tamoxifen sequence is more effective than the reverse [4].

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While some degree of non-cross-resistance undoubtedly exists between endocrine agents, many of the reported observations in the literature are open to criticism because of: (a) observer bias influencing interpretation of objective response, particularly when pain relief is achieved in bone metastases; (b) failure to wait long enough for response to a first agent before moving on to a second agent, and thus ascribing delayed response to the second agent; (c) confusion of withdrawal response to the first agent with positive response to the second; and (d) assessment of response to a second agent being based on clearly recognisable criteria (e.g. in skin metastases) while assessment of response to the first agent is based on less highly developed criteria (e.g. in bone metastases).

The first report suggesting an advantage for combination endocrine therapy was in 1962, when Huggins and his group [5] reported 'extinction' of DMBA-induced rat mammary cancer following the administration of combined oestrogen and progestin. Clinical trials of oral contraceptives containing oestrogen and progestin were subsequently shown to cause tumour regression in some tumours which had either failed or lost response to other hormonal manipulations [6]. However, other trials showed no higher a response rate from the combination than from oestrogens alone.

High-dose oestrogen has also been combined with androgen therapy and with tamoxifen therapy but neither combination has led to a significantly higher response rate than from oestrogen alone [4]. It may be relevant that both androgen and tamoxifen have a lower affinity for oestrogen receptor than does oestrogen itself. Antioestrogens such as tamoxifen have been

combined with other endocrine modalities in randomised trials but without improving on the response rates from tamoxifen alone. Thus combinations with androgens, progestins, bromocriptine or prednisone showed no significant advantage over tamoxifen alone in the treatment of breast cancer, either in response rate or in duration of response [4].

In the case of premenopausal patients, no advantage has been shown from adding bilateral adrenalectomy to oophorectomy as the initial method of endocrine therapy. Still incomplete, however, are trials in which tamoxifen or aminoglutethimide are added to ovarian ablation.

Two endocrine agents are now in the forefront of breast cancer treatment: tamoxifen and aminoglutethimide. A combination of the two has been reported to have no advantage over either one alone, but the addition of a third endocrine agent, danazol, is claimed by one group to have increased the response rate. Others, however, have reported that a combination of aminoglutethimide and danazol *decreased* both response and survival rates compared to aminoglutethimide alone.

SEQUENTIAL COMBINATION OF ENDOCRINE THERAPY

Part of the effect of endocrine therapy on breast cancer may be through an immunological mechanism resulting from changes in the pituitary-adrenal-gonadal axis. Nevertheless, a major part of the effect of endocrine therapy on the growth of human mammary cancer is undoubtedly through hormone receptors in the tumour cells. Steroid receptor protein has been shown in human mammary cancer for oestrogen, androgen, progesterone and glucocorticoids, while cell membrane receptors for prolactin and growth hormone have been reported by some.

There is, however, a complexity in that some steroids are known to have a pharmacological action on breast cancer through receptors other than their own. There is now considerable evidence that progestins can bind to androgen and to glucocorticoid receptors in addition to the progesterone receptor, while androgens can bind to the oestrogen receptor (ER) in addition to androgen receptor (AR). These observations could explain, for example, why the response of breast cancer to progestin therapy does not clearly correlate with the progesterone receptor (PgR) status of the patient's tumour, and why the response to androgen therapy does not clearly correlate with the AR status of the tumour.

Hormones interact also in the regulation of receptor synthesis. While oestrogen stimulates the synthesis of progesterone and prolactin receptor, prolactin stimulates synthesis of oestrogen receptor and tamoxifen temporarily stimulates synthesis of progesterone receptor. Stimulation of hormone receptor synthesis should make cells more sensitive to their respective hormones, and this is the rationale behind trials of progestin therapy after priming by either oestrogen therapy [7] or tamoxifen therapy [8].

While inhibition of mammary cancer growth by most endocrine manipulation probably involves an effect on both ER and PgR, the mechanism by which tamoxifen causes regression of breast cancer may differ from that of the others. Its administration causes a fall in ER level in all cases but a *rise* in the PgR level in the majority. In DMBA-induced rat mammary cancer tamoxifen appears to destroy cells containing both ER and PgR but not those cells containing ER alone [3].

The mechanism by which progestin therapy causes regression of breast cancer is probably also different from that of other modalities. There is no clear evidence for either medroxyprogesterone, norethisterone or megestrol that the likelihood of response is correlated with the presence of ER in the tumour. Again (as in the case of prednisone), response rate does not increase with age or with a history of having responded to other endocrine modalities.

These observations have prompted clinical trials of a combination of tamoxifen and medroxyprogesterone. As reported above, concurrent administration of the two agents yielded no better a response rate than from tamoxifen alone, but the observation that tamoxifen stimulates PgR production has suggested the possibility that medroxyprogesterone therapy might be more effective if used in sequence after tamoxifen. Given alternately for 14 days each, a 59% response rate was reported in 44 patients with advanced breast cancer refractory to conventional therapy [8]. Alexieva-Figusch reverses the sequence by adding tamoxifen after having primed the tumour with megestrol alone for 6 weeks [1].

Further trials are necessary to confirm the ability of alternating tamoxifen and progestin therapy to prolong or restore response in advanced breast cancer. Relative timing of the agents is critical because tamoxifen inhibition of oestrogen receptor leads to *decrease* in PgR synthesis after the first 2 weeks of therapy. Relative timing of the two agents is critical also because of the long half-life of both tamoxifen and medroxyprogesterone in the body. These observations cast doubt on the rationale for alternating tamoxifen and progestin therapy until we have more knowledge on the temporal interactions between these agents and the various steroid receptors in breast cancer.

It has been suggested on the basis of vaginal smear assay that oestrogen may be important as a priming factor for successful progestin therapy in breast cancer [6]. In a small series of advanced breast cancers refractory to conventional hormone therapy, sequential administration of ethinyl oestradiol followed by medroxyprogesterone has been reported to yield some cases of regression of tumour [7]. Again, it is clear that the ratio between oestrogen and progestin levels and their relative timing is likely to be critical in inducing ER of PgR levels which might improve, prolong or restore response in breast cancer.

FUTURE PROSPECTS

We have set up arbitrary clinical criteria to define an acceptable degree of tumour regression following systemic therapy. Using these criteria, approximately 30% of patients with advanced breast cancer will show response following oophorectomy, adrenalectomy, hypophyseal ablation, high-dose oestrogen, anti-oestrogen, progestin or aminoglutethimide therapy. If only those tumours which are oestrogen receptor positive (ER+) are considered, the response rate is about 50% for most modalities.

A similar plateau has been reached in the regression rate from combination cytotoxic therapy in breast cancer but this is set at 50% for unselected cases instead of 30%. One reason for this is that both ER+ and ER- tumours show a 50% likelihood of responding to cytotoxic therapy whereas ER- tumours show only a 10% likelihood of response for endocrine therapy. We are unlikely to improve on the 30% regression rate to endocrine therapy until we can overcome biological limiting factors in breast cancer. These include the biological heterogeneity of the tumour cells in each cancer, the low proportion of proliferating cells in most cancers, unfavourable site factors and poor vascularity in many of the deposits.

The 30% tumour regression rate presently observed for all types of endocrine therapy does not necessarily imply that the same 30% of cases would respond to all modalities. It is, however, highly likely for those modalities where the response rate in ER+ cases is approximately 50%. (These include oophorectomy, adrenalectomy, hypophysectomy, high-dose oestrogen, anti-oestrogen and aminoglutethimide but *not* progestin or corticosteroid therapy.) There are, however, some site differences between the modalities in responsiveness, in that bone metastases are more likely to respond to androgen or aminoglutethimide therapy while soft tissue metastases are more likely to respond to high-dose oestrogen or anti-oestrogen therapy.

There have been very few clinical investigations of the mechanisms by which breast cancer loses its response to endocrine therapy. Two major explanations have been offered for the development of hormonal autonomy: (a) development of homeostatic changes in the host's hormonal balance after its disturbance by therapy; and (b) the metabolic activity of the tumour cells becomes independent of the hormonal environment in the host as a result of selection of cell types which can grow without the supporting hormone.

It is also suggested that response to secondary hormone therapy after *failure* to respond to primary therapy may result from changes in the hormonal balance resulting from an effect of the first therapy on the hypothalamo-pituitary mechanisms of the host [3]. However, no evidence of specific changes in endogenous hormone levels were found to be associated either with response or loss of response to treatment by tamoxifen, aminoglutethimide or danazol [9].

It is believed that human mammary cancers consist of a mixture of oetrogen receptor-positive (ER+) and receptor-negative (ER-) cells [10]. A mixed cell population would explain why remissions in so-called ER+ breast cancers are limited in duration, and the tumour then progresses to an autonomous condition. Although loss of progesterone receptors (PgR) has been observed in most cases of human mammary cancer developing autonomy after primary endocrine therapy, many of the patients with ER+ but PgR- tumours subsequently respond to secondary hormonal therapy [9]. This observation suggests that reactivation of tumour activity during endocrine activity does not necessarily involve outgrowth of clones with a different steroid receptor content.

An alternative possibility is that the tumour growth adapts itself to a changed hormone environment by a change in steroid receptor *interactions*. It has been shown that oestrogen, progesterone and androgen receptors are demonstrable in the same breast cancer cell, and presumably interact by receptor regulatory mechanisms. This may explain why a hormone responsive breast cancer can be repeatedly controlled by a series of hormonal manipulations using different hormones in a sequential manner. But we need to clarify whether primary endocrine therapy should be continued when secondary therapy is started at the appearance of recurrent tumour activity. It could be argued that the recurrent tumour is an outgrowth of resistant clones and that the primary endocrine therapy needs to be continued to keep the originally dominant clone under control.

Finally, the question of whether we can induce hormone sensitivity in breast cancer. The

response rate to endocrine therapy increases with increasing ER content of breast cancer. Various agents such as vitamin A and the retinoids have been shown to be important in tumour cell differentiation and to have a strong anti-proliferative effect. We have yet to determine whether such agents can increase the proportion of ER+ clones in breast cancer and thus improve, prolong or restore response to endocrine therapy.

The duration of response to current endocrine modalities is determined by cytokinetic factors arising from: (a) variability between patients in the proportion of proliferating cells to stroma; and (b) biological heterogeneity among tumour cells of each cancer [2]. Although we have so far not evolved a combination of endocrine agents which clearly prolongs response, it is possible that improved timing of agent administration may be effective in this respect, e.g. by intermittent therapy using the *same* agent [11]. All new strategies will need to be controlled by serial measurements of tumour burden and its relative proportion of ER+ and PgR+ cells and this may soon be possible by the application of existing monoclonal antibody techniques [12].

CONCLUSION

Cytokinetic reasons probably explain why concurrent combinations of presently available endocrine agents do not appear to increase the regression rate in breast cancer beyond that resulting from one agent alone. Priming of breast cancer by suitable endocrine agents may increase hormonal sensitivity in previously resistant clones of a tumour or restore hormonal sensitivity when clinical response is lost, but relative dosage and timing of the agents may be critical. In order to evaluate strategies for improving, prolonging or restoring response in a tumour under treatment, we will need ways of serially measuring total tumour burden and its relative proportion of ER+ and PgR+ cells. Suitable monoclonal antibody techniques are becoming available for this.

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