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ENDOCRINOLOGICAL AND CLINICAL ASPECTS OF LHRH ACTION (ICI 118630) IN HORMONE DEPENDENT BREAST CANCER

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Summary—The effect of an LHRH agonist, D-Ser (Bu^t)^{6}Azgly^{10}-LHRH (Zoladex®, ICI 118630) on pituitary gland and ovarian function has been investigated in patients with advanced breast cancer. In both pre and postmenopausal women ICI 118630 produced a substantial rise in circulating concentrations of gonadotrophins within 2 h of the first injection. However, on continued exposure to the drug plasma LH and FSH levels decreased to below pre-treatment values (14–21 days). This was especially evident in postmenopausal women. In premenopausal patients plasma progesterone and estradiol levels were significantly reduced after 2 and 4–6 weeks of therapy respectively, reaching values observed in oophorectomized or postmenopausal patients. No substantial acute or long-term influence of the drug on these hormones was seen in postmenopausal women. Breast tumor remissions were recorded primarily in premenopausal patients with estrogen receptor positive tumors. No responses were seen in patients with estrogen receptor negative disease. Minimal side effects were recorded.

INTRODUCTION

A rapidly expanding series of publications on the use of luteinizing hormone-releasing hormone (LHRH) agonists as anticancer agents is currently appearing in clinical literature. The majority of these studies represent the early steps which are necessary for the testing of new drugs and are designed to evaluate the endocrine actions of LHRH agonists at different dose levels, assess their toxicity and identify clinical remissions. These studies must of course be carried out against a background knowledge of the disease itself and the impact existing therapies have on its progression. In this way evidence for either novel or adverse actions of the drugs may be tentatively identified and exploited or rectified. Since the rationale for the use of LHRH agonists in the treatment of hormone dependent cancer of the breast originate in their ability to elicit a chemical castration-like response in the gonads of animals, it is timely to attempt a preliminary endocrinological and clinical comparison of the effects of LHRH agonists with those resulting from oophorectomy in women. The present communication undertakes such a comparison for Zoladex (ICI 118630; D-Ser(Bu^t)^{6}Azagly^{10}LHRH).

Endocrine effects of Zoladex in premenopausal women with breast cancer

The endocrine effects of Zoladex on circulating levels of ovarian and pituitary hormones have been extensively reviewed elsewhere [1, 2]. In the present communication these data will be summarized in an updated form.

The patients selected for the study were those with histologically proven carcinoma of the breast who had either recurrent or locally advanced disease and were premenopausal. No patient was entered into the study who had received prior ablative or additive endocrine therapy for either their primary or recurrent disease. Zoladex (supplied by ICI Pharmaceuticals Division, Macclesfield, U.K. in 1 ml ampoules containing 500 μg of the drug in citrate buffer adjusted to pH 5) was administered daily (500 or 1000 μg/day) by subcutaneous (s.c.) injection during the morning. Treatment was initiated in the breast clinic of R.W.B. As a consequence of this and the requirement for prompt therapy, an important feature of the study was that Zoladex treatment was started at various stages of the menstrual cycle.

The patterns of luteinizing hormone (LH) and follicle stimulating hormone (FSH) released during treatment with the LHRH agonist were qualitatively similar in individual patients and appeared largely independent of whether treatment was initiated during the follicular or luteal phases of the menstrual cycle. Thus, elevated gonadotrophins were observed in all patients after the first injection of the drug and were followed by a subsequent reduction in their basal values during the first and second menstrual cycle. Pituitary gland sensitivity to Zoladex was examined on day 1 of treatment and after long-term therapy (60 ± 22 days). The data indicated that whereas within 4 h of the initiation of therapy on day

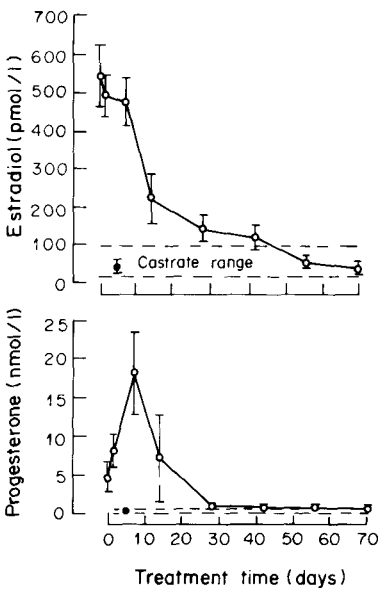

Fig. 1. Influence of Zoladex (ICI 118630) and castration on plasma levels of estradiol and progesterone in premenopausal patients with advanced breast cancer. ICI 118630 (500 or 1000 μg) was injected daily for 70 days in 15 premenopausal patients. Plasma samples were removed at the times indicated 24 h after the last injection of the drug and assessed for estradiol and progesterone by radioimmunoassay. The data are expressed as a mean value SEM and are compared with a range of hormone values determined in 6 control patients (postmastectomy) 2 months after the surgical removal of their ovaries.

1 plasma LH and FSH concentrations rose from 5.4 ± 3.42 U/l ($n = 7$) and 3.5 ± 1.77 U/l ($n = 7$) respectively to reach 59 ± 18.6 U/l and 28 ± 13.34 U/l, the corresponding 4 h post-injection values after multiple injections of the LHRH agonist were 0.86 ± 0.42 U/l ($n = 5$) and 2.98 ± 2.03 U/l ($n = 5$). Pituitary desensitization to the releasing hormone activity of Zoladex had therefore occurred.

Small rises in circulating estradiol and progesterone were often associated with the early increased plasma concentrations of the gonadotrophins. This was especially evident when therapy was initiated during the follicular phase of the menstrual cycle. In these women, on continued treatment, while plasma progesterone fell back to levels observed during the early follicular phase of control cycles, estradiol concentrations continued to increase. The levels obtained, however, were indistinguishable from control late follicular phase samples. No evidence of ovulation or formation of an active corpus luteum was seen in these patients since plasma progesterone remained low. Plasma estradiol concentration decreased towards menstruation and were low (< 30 pg/ml; $n = 9$) during the remaining study period (mean duration of treatment 92 ± 17.5 days). No further menstrual activity was observed in these women.

Initiation of Zoladex therapy during either the mid-cycle or luteal phase of the menstrual cycle did not appreciably affect circulating estradiol or progesterone in that cycle. Follicular estradiol production, albeit reduced, was evident during the next cycle and was recorded in the absence of significant plasma progesterone levels. On continued treatment suppressed circulating concentrations of estradiol and secondary amenorrhoea were established in all patients (mean duration of treatment 142 ± 42 days).

Zoladex therapy has been maintained in 3 women for periods approaching 1 year; they continued to show suppressed circulating concentrations of estradiol and progesterone.

The influence of Zoladex on the endocrine status of patients was evaluated at 2 dose levels 500 and 1000 μg/day. No evidence of a differential effect was recorded.

Comparative effects of Zoladex and castration in premenopausal women

Surgical removal of the ovaries results in a very rapid decline in circulating levels of estradiol and progesterone [3] and immediate cessation of menstrual activity. Thus within 7 days of a bilateral oophorectomy the plasma concentrations of these hormones have reached those normally recorded in postmenopausal women who have undergone a natural menopause [4]. Similarly, low estradiol and progesterone values were rapidly achieved in Zoladex treated patients, although the plasma concentration of estradiol did not reach absolute castrate values in some patients for approx 8 weeks (Fig. 1). A small initial rise in plasma progesterone levels was observed on day 7 of Zoladex therapy. The levels recorded were however low in comparison with control mid luteal phase samples (50–80 nmol/l). These data were reflected in the inability of the drug to uniformly establish an early secondary amenorrhoea.

It is evident that under the present conditions Zoladex, together with other LHRH agonists [3] require longer than surgical castration to establish early postmenopausal plasma concentrations of estradiol and progesterone.

Comparative effects of Zoladex therapy and castration on the clinical progression of breast cancer

Clinical responses in premenopausal women. The effect of a beneficial response to oophorectomy in patients with advanced breast cancer is 2-fold. Firstly, offensive lesions regress with amelioration of previously distressing symptoms and secondly, life is prolonged. It is noteworthy, however, that control of the malignant growth is never permanent and recrudescence of the disease always occurs. The principal function of this therapy is therefore palliative and should be achieved with minimum distress to the patients.

There are many conflicting reports in the literature as to the proportion of patients who undergo a remission of their disease after an oophorectomy. Nissen-Meyer[6] in his monograph on castration in breast cancer, quoted the results from 15 centers in

which the remission rate varied between 15.2 and 50%. Such variation undoubtedly reflects the stringency of criteria used to define a response. In our own and as yet small series in which strict criteria of response have been applied [7] the overall response rate to surgical oophorectomy is 25% (8/32 patients). These patients enjoy a mean duration of remission of about 2 years. The responses are confined to women with estrogen receptor positive breast cancers (8/19; 42%); no patient with estrogen receptor negative disease has shown a worthwhile remission (0/13).

To date 15 patients have been evaluated for their response to Zoladex and will be reported in detail elsewhere [8]. Briefly tumor remissions lasting a minimum of 6 months have been observed in 3 women (20%), each with estrogen receptor positive disease. No patient with estrogen receptor negative breast cancer has yet responded to Zoladex therapy. Of the 12 women who failed to respond to Zoladex, 11 have subsequently failed to benefit from the surgical removal of their ovaries. In the remaining woman, her disease regressed after oophorectomy.

These data, although preliminary, do not provide any evidence for differing modes of action for Zoladex and oophorectomy in women with breast cancer. The patient classified as having progressive disease during Zoladex therapy and who subsequently benefited from oophorectomy ceased LHRH therapy after only 70 days of treatment and after only approx 1 month of castrate levels of estradiol.

Clinical responses in peri- and post-menopausal women. The menopausal status of breast cancer patients has an obvious and profound influence on clinical response rate to oophorectomy. Several studies have now reported that the likelihood of a patient obtaining a worthwhile improvement in their disease after oophorectomy decreases progressively with increasing time from the cessation of menstruation [9, 10]. Very little benefit may be expected beyond the 5-year mark. These clinical observations correlate with the transition of the perimenopausal ovary towards its relative quiescent state in the postmenopausal women. In this light, it is surprising that the LHRH agonist, leuprolide, has been reported in a preliminary communication to produce tumor remissions in 12/31 postmenopausal women with metastatic breast cancer which lasted in excess of 10 weeks in 5 patients [11]. Likewise, Mathe *et al.*[12] has reported a 70% regression of tumor mass and disappearance of an axillary node metastases in a postmenopausal patient treated with D-Trp^{6}LHRH for 3 months.

To date Zoladex has been administered (250 μg/day s.c.) to 6 postmenopausal women with asymptomatic breast cancer [13]. Of these women, one patient whose Tc 99 methylene diphosphate (MDP) bone scan was positive at multiple sites in the axial skeleton (typical of bone metastases), has shown clear evidence of regression of metastatic deposits.

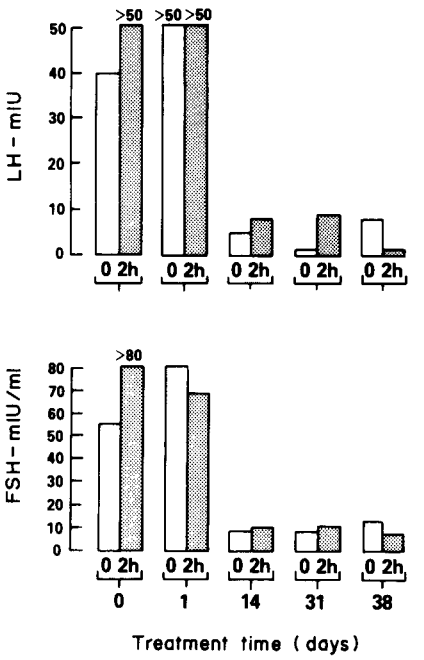

Fig. 2. Influence of Zoladex (ICI 118630) on plasma levels of LH and FSH in a postmenopausal woman with asymptomatic breast cancer. ICI 118630 (250 μg) was injected daily for 38 days in a 58-year old woman (6 years following spontaneous menopause). Plasma samples were removed immediately before and 2 hours after administration of the drugs on the days indicated and assayed for LH and FSH.

The patient was 6 years postmenopausal (spontaneous menopause) and initially presented with an inflammatory T4 breast carcinoma that was estrogen and progesterone receptor positive. Plasma gonadotrophin concentrations in this patient although high at the initiation of therapy, were raised after a single injection of Zoladex (Fig. 2). These elevated levels were maintained on day 2. After 14 days of treatment, however, the circulating concentrations of LH and FSH were considerably reduced and remained low during the remaining period. Basal plasma prolacting concentrations were increased on continued Zoladex therapy, although the concentrations achieved remained within the normal range for postmenopausal women (not illustrated). The LHRH agonist was without effect on the already low plasma concentrations of estradiol and progesterone (Fig. 3). Similarly, no consistent changes were observed in circulating testosterone, dehydroepiandrosterone sulphate and growth hormone. The endocrine effects of Zoladex on the remaining patients who failed to respond to the drug were largely identical to those described above.

These data are consistent with extragonadal actions of the LHRH agonists in postmenopausal women and require verification in a larger group of patients.

Side-effects and formulation of Zoladex

Besides therapeutic effectiveness quality of remission is a major concern especially in patients who

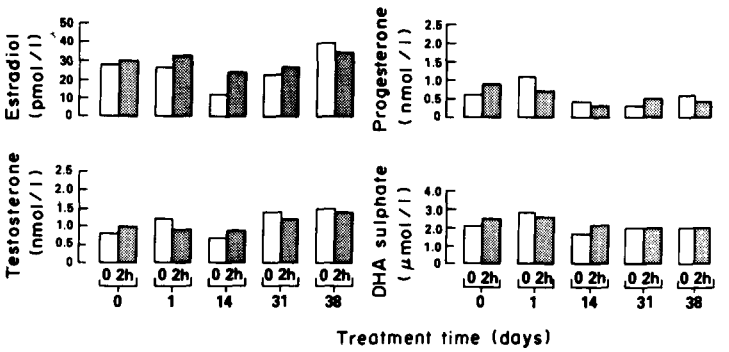

Fig. 3. Influence of Zoladex (ICI 118630) on ovarian and adrenal hormone levels in a postmenopausal woman with asymptomatic breast cancer. Details as in Fig. 2. Plasma samples were assayed for estradiol, progesterone, testosterone and dehydroepiandrosterone sulphate.

experience long-term amelioration of their disease symptoms. In the present series of patients no major side effects or reactions have been noted. Although patients have reported hot flushes and decreased libido, effects common to oophorectomy, the drug has been well tolerated and shows considerable promise as safe therapeutic agent.

The major disadvantage of LHRH agonists, however, is their relative lack of oral activity. In order to overcome this the present study used daily injections of the material. Unfortunately, this is time consuming and inconvenient for the patient. More recently a depot formulation of Zoladex has been developed by ICI (U.K.) which allows the administration of the drug as a single monthly injection [14]. The preparation consists of a 50:50 lactide–glycolide copolymer into which the drug is incorporated. On exposure to body fluids, the copolymer degrades into glycolic and lactic acid, resulting in a continuous release of the LHRH agonist over 28 days. Early trials in male patients with prostatic cancer have shown that the formulation is immediately active, stimulating pituitary release of LH within 1 h of injection and desensitizes the pituitary gland to LHRH within 15 days [15]. Furthermore, the monthly depot preparation is more effective than daily injections of the drug at equivalent dose levels. Thus the ease of administration of the depot formulation of Zoladex together with its increased potency should ultimately benefit the patient suffering from breast cancer and also aid patient compliance. Studies to this end are currently underway in pre-, peri- and postmenopausal women.

Action of Zoladex in breast cancer patients and future prospects

It is clear from the above studies that this long-term therapy (4–8 weeks) of premenopausal breast cancer patients with Zoladex reduces ovarian activity thereby producing and maintaining castrate concentrations of both estradiol and progesterone in plasma (Fig. 1). The most likely explanation for this relative quiescent state within the ovary relates to the ability of LHRH agonists, when administered at high concentrations, to down regulate pituitary LHRH receptors [16] and hence desensitize the pituitary gland to the releasing hormone properties of the drugs [16, 17, 18]. This process eventually results in a fall in circulating levels of LH and FSH and thus a withdrawal of support for gonadal steroidogenic activity [19]. It is noteworthy, however, the pituitary gland desensitization is not an instantaneous event and that the initial action of these drugs is to promote substantial release of LH and FSH. This may lead to two opposing early actions on the ovary, an initial stimulation of estradiol and progesterone production, followed by a loss of receptors for LH and FSH [20, 21], the latter phenomenon decreases the sensitivity of the tissue to gonadotrophins. Unfortunately, it is not possible from the present data to assess critically the relative contribution of each of these actions of LHRH agonists to the rapidity with which Zoladex causes a loss of ovarian secretory activity, although it is evident that a failure to achieve a full pituitary gland desensitization may, in some patients, be associated with persistent follicular activity [2].

The present endocrinological and clinical data using Zoladex in premenopausal women with breast cancer do not offer evidence for any novel actions of the drug other than those already described. Continued studies in postmenopausal women may however prove rewarding. Our data, although preliminary, imply actions of Zoladex on tumor growth in addition to those normally determined by routine hormone measurements. Thus while it is possible that a more dynamic sampling procedure may unravel the complexities of LHRH action on the hormonal environment of tumors in postmenopausal women, it is also feasible that these drugs may have inherent antitumor activity themselves. Certainly, the latter hypothesis has some [22] although not universal [23, 24] experimental support. Clearly much more clinical, endocrinological and experimental data are required to resolve this important question.

In the immediate future it is likely that the main clinical value of the class of drugs to which Zoladex belongs will center around their inability to elicit a chemical castration-like response within the ovaries

of premenopausal women. Attention must therefore be focused on establishing this effect as quickly as is feasible, as a failure to do so may limit their clinical usefulness and may explain why women whose tumor apparently progressed during Zoladex therapy subsequently responded to oophorectomy. In this context it is noteworthy that many clinicians now desist from using an X-ray induced menopause in the therapy of rapidly progressing breast cancer and in patients with severe pain. This is not a consequence of the inability of ovarian irradiation to reduce circulating estradiol and progesterone to values seen in surgically castrated patients, but because the effects are produced much less rapidly than surgery. These patients often experience persistent ovarian activity for up to 3 months, during which time disease control may not be fully established. Since the depot preparation of Zoladex is more effective than the daily injection of equivalent amounts of the LHRH agonist [13] studies to examine its early effects on ovarian function are currently underway.

If this can be resolved LHRH agonists will find a role as non-invasive and nontoxic alternatives to the surgical removal of the ovaries in premenopausal women with breast cancer. Application of these agents in the treatment of the postmenopausal disease remains a tentative yet exciting possibility.

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