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Treatment of pre-menopausal advanced breast cancer with goserelin—a long-acting luteinizing hormone releasing hormone agonist

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Twenty-two pre-menopausal evaluable patients with advanced breast cancer (median age 39 years; ER positive 19, unknown three; prior adjuvant chemotherapy 16) were treated with the LHRH agonist goserelin depot (Zoladex*). Serum levels of 17 β-estradiol and progesterone were suppressed by goserelin within 3–4 weeks of therapy, while serum leuteinizing hormone and follicle stimulating hormone titers remained in the low level of the normal range. Complete or partial response was documented in seven of 22 cases (32%) and occurred in all major sites of disease. Tumor response was documented in women regularly menstruating at the start of therapy. Median time to disease progression was 23 weeks; median duration of response was 64 weeks; overall survival was 141 weeks. Zoladex was well tolerated: only hot flushes in 82% and reversible cutaneous pigmentation in the site of injection in 45% of the patients were observed. In our experience the activity of Zoladex was comparable to that of oophorectomy, without the psychological trauma and the morbidity related to surgical castration.

Key words: Breast neoplasm, luteinizing hormone releasing hormone agonist, metastatic disease.

Introduction

Deprivation of estrogens obtained by surgical castration is able to induce tumor regression in pre-menopausal women with hormone dependent breast cancer. The response rate of about 30% in unselected patients is reported to rise to 50% in women with estrogen receptor (ER) positive tumors.[1,2] Less invasive methods to achieve a castration-like condition have been sought. Recent observations that luteinizing hormone releasing hormone (LHRH) agonists, when given chronically at supraphysiologic doses, have the ability to suppress ovarian steroidogenesis suggest that these molecules might be ideal drugs for producing medical castration.[3,4] The inhibitory effect exerted by LHRH analogs on ovarian function occurs because of the desensitization of the pituitary LHRH receptors induced by these drugs. Following an initial stimulation of gonadotropin secretion, the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) is blocked and the circulating levels of estradiol and progesterone fall, after 3–4 weeks, to the values observed after surgical castration[5,6] and remain at these concentrations as long as the treatment is continued.[7–10]

Materials and methods

Patient selection

From April 1987 to February 1989, 22 pre-menopausal patients with advanced breast cancer were selected for the treatment with the LHRH agonist goserelin, either on the basis of ER-positive assay from primary tumor or accessible metastatic lesions; or, in the absence of these data, by established clinical criteria of potential endocrine dependence (e.g. disease free interval greater than 2 years). All patients had neither been previously

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Table 1. Pretreatment characteristics of evaluable patients

Number	22
Median age (range)	39 (28–52)
Regularly menstruating	18 (82%)
Last menstrual period < 1 year	4
Estrogen receptor status	
positive	19 (87%)
unknown	3
Disease-free interval	
<24 months	9 (41%)
>24 months	13 (59%)
Prior chemotherapy[a]	16 (73%)
Dominant site of disease	
soft tissue	6
bone	11 (50%)
viscera	5

[a] Adjuvant CMF, 14 patients; neoadjuvant FAC, two patients.

treated for their metastatic disease nor subjected to previous hormonal manipulation. Previous chemotherapy included adjuvant CMF (cyclophosphamide, methotrexate and fluorouracil) in 14 patients and FAC (fluorouracil, adriamycin and cyclophosphamide) for locoregional disease in two patients. The ECOG/WHO performance status was <2.[11] All patients had normal peripheral leukocyte and platelet counts without severely impaired liver and renal function tests. The pretreatment characteristics of the 22 evaluable patients are reported in Table 1.

Treatment plan

Zoladex depot, containing 3.6 mg of goserelin, was supplied by ICI Pharma, ready for use in a pre-filled applicator. The drug was administered by s.c. injunction every 4 weeks. A minimum of 3 months of therapy was required for treatment response to be assessed. Therapy was continued until measurable tumor progression was documented. Pretreatment assessment included physical examination with measurements in centimeters of all neoplastic lesions, chest X-ray, bone scan and skeletal survey if indicated, liver echotomography in the presence of hepatomegaly or abnormal liver function tests, complete blood count and biochemical profile. Physical examination was repeated every 4 weeks, i.e. before each drug administration. Radiological studies and hematochemical tests were repeated every 2–3 months or whenever indicated by the individual clinical situation.

Hormone assay

Pituitary and ovarian activities were evaluated before and during treatment with Zoladex. In the first nine patients LH, FSH, 17β-estradiol and progesterone were determined in plasma samples collected just before starting treatment, and then 3, 7 and 14 days after the first drug administration. Samples were also collected before each depot for the first 3 months, and then bimonthly and at the end of therapy. Plasma samples were stored at $-20^{\circ}C$ until assayed. Plasma concentrations of 17β-estradiol, progesterone, LH and FSH were measured using commercially available kits. Intra and inter coefficients of variation of quality control pools were 4–7, 7–11.2, 2.7–5 and 1.7–4.6% for 17β-estradiol, progesterone, LH and FSH, respectively. The sensitivities of the methods used for each hormone were the following: 17β-estradiol, 5 pg/ml; progesterone, 0.1 ng/ml; LH and FSH, 1 mU/ml.

Response evaluation

Treatment response was assessed according to the standard WHO criteria.[11] Complete response (CR) was defined as complete disappearance of all measurable tumors, with no new lesions being recorded; in the presence of lytic bone metastases these had all to be recalcified or to have disappeared at bone scan. Partial response (PR) required a reduction of greater than 50% in the sum of the products of the longest perpendicular diameters of measurable tumor lesions and objective evidence of improvement in evaluable but non-measurable lesions, with no new lesions appearing. It was not necessary for every tumor lesion to have regressed to qualify as PR, but no single lesion should have progressed. No change or stable disease (SD) indicated a less than 50% decrease or a less than 25% increase in the sum of the products of the longest perpendicular diameters of measurable lesions for a minimum of 2 months. Disease progression (PD) was defined as an increase of more than 25% over the original measurement in the product of the two longest perpendicular diameters of measurable tumor lesions and/or the appearance of new disease manifestations. Duration of response and survival were calculated, by Kaplan and Meir methods,[12] in months from the beginning of treatment to the day of documented progressive disease and/or death.

Table 2. Response according to single site of disease

		CR	PR	AD	PD
Soft tissue					
breast	2			2	
nodes	14	3	—	4	7
skin	8	1	—	3	4
Viscera					
lung	3	2	—	1	—
pleura	1	—	—	—	1
liver	1	—	—	—	1
Bone	12	—	3	3	6

Table 3. Objective responses according to selected parameters

	No. of patients	CR + PR
ER		
positive 10–50 fmol	12	4
positive >50 fmol	7	1
unknown	3	2
Disease free interval		
<24 months	9	1
>24 months	13	6 (46%)
Prior chemotherapy		
yes	16	3 (19%)
no	6	4 (65%)
Age		
<35 years	3	0
>35 years	19	7 (37%)

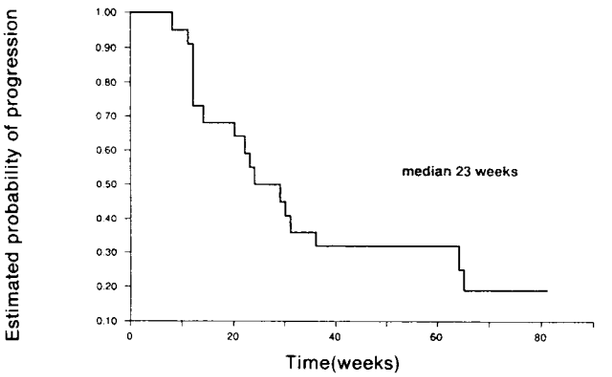

Figure 1. Lifetable median time to progression in all patients.

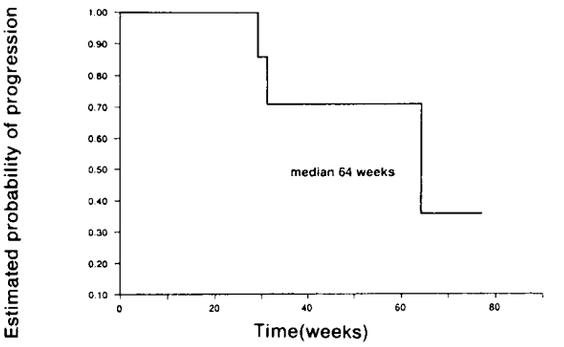

Figure 2. Lifetable median duration of response in responding patients.

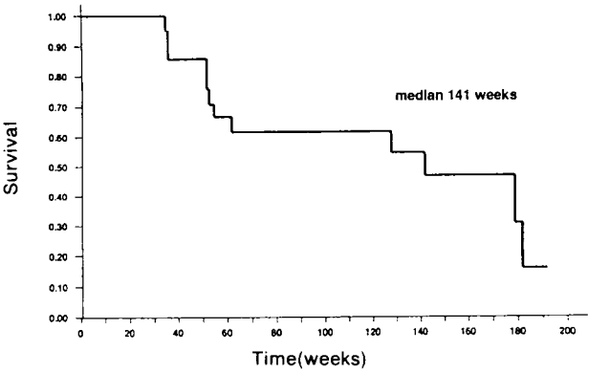

Figure 3. Lifetable median overall survival in all patients.

Results

Clinical response

Five of 22 evaluable patients achieved a complete tumor response and two a partial response. Disease stabilization or minimal response was observed in other five women. One of these patients showed a dramatic improvement of bone pain for 17 months, although the osseous lesions remained radiologically unchanged. Therefore, the overall response rate, CR + PR, was 32%. CR or PR was observed in all major disease sites as detailed in Table 2. In the present series (Table 3), objective tumor response was not influenced by ER concentration, but it was markedly affected by duration of disease free interval and prior chemotherapy. In fact, objective response was documented only in one of nine patients who showed relapse within 2 years from local regional treatment, compared to six of 13 women with a longer disease free interval (46%). Similarly a higher percentage of response was observed in untreated, compared with previously treated patients (65% versus 19%). All responses were documented in patients who, at the start of treatment, had regular menses and were over 35 years of age. Delayed amenorrhea, i.e. cessation of menses beyond the second month of treatment with

Zoladex, was recorded in five patients. However, this event failed to influence treatment response.

Median time to disease progression for all patients (Figure 1), estimated by the Kaplan and Meier method[12], was 23 weeks (range 8–81), while median duration of response (Figure 2) was 64 weeks (range 29–77). Median overall survival, for all patients, given in Figure 3, was 141 weeks (range 35–182). Following Zoldex treatment, toxicity was mild and mainly represented by hot flushes, as a consequence of the chemically induced menopausal status (82%). Cutaneous dyschromia, at the site of drug injection, occurred in 45% of cases and was reversible after few months. No alterations of hepatic or renal function tests were detected. A weight gain of about 3 kg was observed in 12 patients. Oophorectomy performed in four of nine non-responding patients was not effective. Tamoxifen and aminoglutethimide were also ineffective in the remaining five patients who failed to respond to Zoladex.

Endocrine effects

The effects of monthly s.c. injections of Zoladex depot for three consecutive months on plasma concentrations of 17β-estradiol, progesterone, LH and FSH in nine patients are shown in Figures 4 and 5.

The pretreatment plasma concentrations of 17β-estradiol were very variable ranging from above castration levels (30 pg/ml) to menopausal levels (Figure 4a). During the first 3 weeks of treatment, plasma concentration of 17β-estradiol decreased gradually, and by the third week the steroid levels fell into the range of castration values, after a temporary rise observed within the second and third week in three patients. Plasma levels of 17β-estradiol concentrations remained suppressed during the subsequent months, until cessation of treatment, and were comparable to those observed in post-menopausal women. Figure 4(b) illustrates the effects of Zoladex on the concentration of circulating progesterone. After a rise in progesterone levels, recorded during the first week of treatment in three patients, hormone levels decreased by the second week and consistently low concentrations were found in all subsequent plasma samples (<2.5 ng/ml).

Figure 5(a) reports the plasma levels of LH in patients treated with Zoladex depot. Two subgroups of patients may be identified. The first consists of four subjects who had high pretreatment

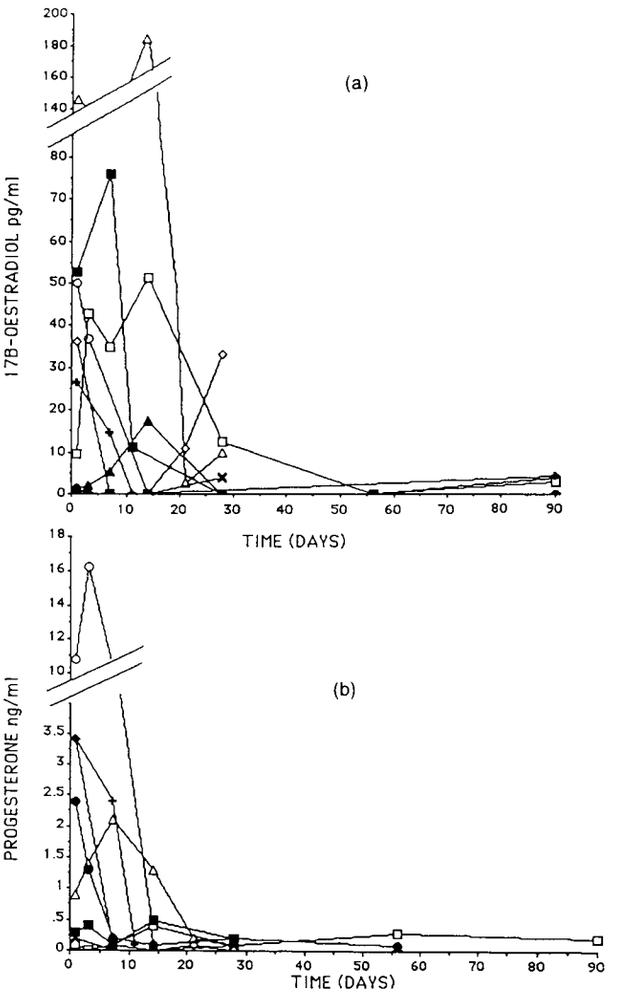

Figure 4. Effect of monthly s.c. injection of Zoladex depot for three consecutive months on plasma concentrations of (a) 17β-oestradiol and (b) progesterone in nine premenopausal patients with advanced breast cancer.

LH levels and the other includes five patients with low plasma levels of LH. In the latter subgroup, at least in three patients, treatment induced a rise in plasma LH levels during the first week of drug administration. The concentrations of circulating LH gradually declined during the first month in both the subgroups reaching a value of about 8–10 mU/ml (values in normal subjects 5–20 mU/ml) which was maintained throughout the treatment period. A profile similar to that observed for LH has been obtained for FSH (Figure 5b). The decrease in the concentration of FSH was, however, greater and prompter than that observed for LH. Seven patients were maintained on Zoladex therapy for a period exceeding 1 year with suppressed

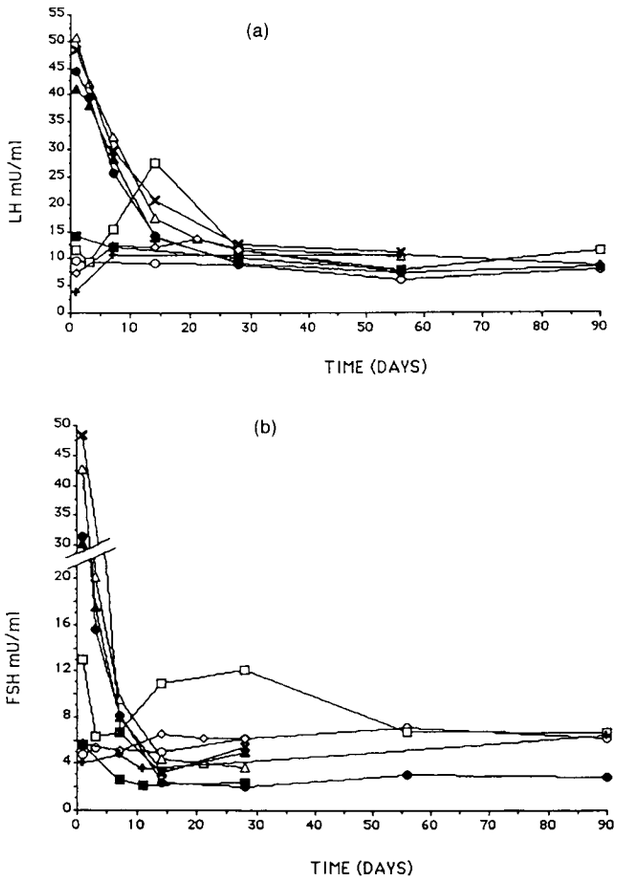

Figure 5. Effect of monthly s.c. injections of Zoladex depot for three consecutive months on plasma concentrations of (a) LH and (b) FSH in nine pre-menopausal patients with advanced breast cancer.

circulating concentrations of all the hormones assayed.

Discussion

In this study, monthly s.c. injections of a potent LHRH agonist, Zoladex depot, proved to be effective in one-third (seven of 22) of pre-menopausal women with metastatic breast cancer with minimal side effects. This finding is in agreement with the data reported in the medical literature, using either Zoladex or different LHRH agonists,[7,10,13,22] and with similar series treated in our Institution with surgical castration. Our experience with oophorectomy performed as first salvage treatment in pre-menopausal women relapsing after adjuvant chemotherapy, showed an objective response rate of 21%[23]. The length of disease free interval was a prognostic factor correlated with response: when it was longer than 2 years, the response rate to treatment with Zoladex was 45%. All responses have been documented in women regularly menstruating at the beginning of therapy. All sites of disease responded to treatment, including visceral metastases, with complete disappearance of lung nodular metastases in two patients. Compliance was excellent by all patients. The subsequent oophorectomy performed in patients failing Zoladex was unsuccessful, confirming the predictive value of the initial endocrine response.

Complete suppression of ovarian activity was obtained in all patients after 1–2 months of treatment with Zoladex. On continued treatment, and as long as therapy lasted, plasma levels of 17β-estradiol and progesterone were maintained suppressed. The effect of Zoladex on LH and FSH secretion was less pronounced. The inability of Zoladex to totally suppress gonadotropin secretion might be suggestive of the following hypotheses: (1) the amounts of LH still present in the plasma samples relates to the radioimmunologically assayable gonadotropin and not to the biologically active peptide[25] or (2) the effect of the LHRH agonist might also be directed on gonadal tissue.[26,27] The variability of the endocrine responses, which occurred during the first 3 weeks of therapy, seems to be independent of the time of the menstrual cycle during which treatment was initiated.

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