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CAF* and Nasal Buserelin in the Treatment of Premenopausal Women with Metastatic Breast Cancer

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Abstract—*This study was undertaken to determine whether intranasally administered buserelin, a gonadotrophin releasing hormone analog agonist, can be given with CAF to premenopausal women with advanced and/or metastatic breast cancer, and to assess toxicity and therapeutic effect. Of 24 women entered into the study 22 were evaluable; objective responses were documented in 18 patients (seven CR and 11 PR). The median time to treatment failure was 402 days. Buserelin, given with CAF, was well tolerated with the only additional side-effect being hot flushes. Amenorrhea occurred in 13/17 menstruating women and serum estradiol levels decreased to postmenopausal values in all patients.*

INTRODUCTION

SURGICAL REMOVAL of the ovaries for the management of metastatic breast cancer in premenopausal women was first reported in 1896 [1] and remained the standard approach in premenopausal women for decades. A review of major reports on surgical castration show remission rates of 24–37%, and if more rigid criteria of response are used response rates tend to be lower [2]. During the past 15 years it has been convincingly shown by large cooperative studies that significantly better partial and complete remissions are obtained when cytostatics are used in conjunction with oophorectomy [3, 4]. In an ECOG study a response rate of 80% was obtained for premenopausal women with ER positive or ER unknown disease treated with oophorectomy plus CAF and in premenopausal women with ER negative disease treated with CAF without oophorectomy the response rate was 70% [4].

Oophorectomy is associated with some morbidity and some psychological problems. An alternative method of medical castration has recently been introduced. Synthetic gonadotrophin-releasing factor analogs have been shown to result in supraphysiological gonadotrophin release; with repeated administration their effect is paradoxical, the synthesis and secretion of gonadotrophins is decreased and gonadal hormone concentrations fall [5]. It has been demonstrated that intranasal administration of an LHRH analog throughout the menstrual cycle will cause anovulation [6]. Activity has been demonstrated with buserelin (D-Ser[Bu] LHRH ethylamide) in premenopausal women with breast cancer [7].

This study was undertaken to evaluate the therapeutic effects and side-effects when buserelin is given with cyclophosphamide, doxorubicin and 5-fluorouracil (CAF).

MATERIALS AND METHODS

Twenty-four women with histologically confirmed advanced and/or metastatic breast cancer were included in this study; the median age was 40 (range, 32–57 years). Five of the patients had had a hysterectomy, but all 24 were premenopausal, as determined by serum hormone levels. The mean baseline serum estradiol was 290 pmol/l, with a range of 20–1150; there was correlation between serum estradiol level and age ($P = 0.055$). The mean FSH was 24 IU/l (range, 2–99.5) and the mean LH was 39.5 IU/l (range, 1–175). Performance status according to Eastern Cooperative Oncology Group (ECOG) [8] classification was PS 0 in seven women, PS 1 in 14, PS 2 in two and PS 3

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*CAF = cyclophosphamide, doxorubicin, 5-flourouracil.

in one patient. Patients who had prior chemotherapy for metastatic disease were not eligible; seven patients had received prior adjuvant chemohormonotherapy with CMFPT; in these seven patients disease recurred after the adjuvant treatment had been completed and a period of at least 2 months had elapsed after the last dose of adjuvant treatment.

Patients had to show evidence of adequate renal and hepatic function (unless the hepatic abnormality was considered to be due to metastatic involvement), i.e. (1) creatinine level <1.5 mg/dl, (2) bilirubin level <1.5 mg/dl and (3) SGOT concentration <100 IU/ml. If the creatinine value was >2, the bilirubin value >5 or the SGOT value >600, the patient was not eligible. Patients also had to have WBC >4000/ul, a platelet count >100,000/μl, unless there was a documented marrow involvement by tumor. All patients agreed to sign appropriate informed consent forms.

Patient ineligibility criteria included failure to meet any of the criteria mentioned before, patients with a history of malignant neoplasms other than curatively treated basal cell carcinoma of the skin or carcinoma *in situ* of the cervix, and patients who were medical or psychiatric risks or who had nonmalignant systemic disease that would preclude their being subjected to any of the treatment options, e.g. heart disease and doxorubicin therapy.

Estrogen receptor status was positive in nine patients, negative in six and unknown in nine. Dominant disease sites were as follows: 13 patients had skeletal metastases (three bone only, eight bone and visceral, two bone and soft tissue), three patients had visceral metastases (lung and/or liver), seven patients had soft tissue metastases and in one patient the dominant disease site was the central nervous system.

Treatment consisted of six cycles of induction with CAF (cyclophosphamide 100 mg/m^2 p.o. d1–14 doxorubicin 30 mg/m^2 i.v. d1 and d8 and 5-fluorouracil 500 mg/m^2 i.v. d1 and d8) repeated every 28 days. Concomitantly the patients received the gonadotrophin hormone-releasing hormone agonist, buserelin, intranasally. The nasal spray was so constituted that a single inhalation delivered 100 mcg of GnRHA. The dose administered was 2400 mcg/day × 7 days (two inhalations in each nostril six times a day for a total of 24 inhalations/d). After day 8, the patients received 1200 mcg/d of buserelin (two inhalations in each nostril three times a day for a total of 12 inhalations/d). If evidence of disease progression occurred at any time after a minimum of 28 days of treatment, patients were removed from the study. In patients who were not yet in CR (complete remission) after six cycles of CAF the doxorubicin was replaced by methotrexate 40 mg/m^2 d1 and d8.

RESULTS

Of 24 patients participating in the study, 22 were evaluable for response and toxicity. Two patients refused treatment after 7 and 10 days respectively. The median observation time for the 22 evaluable patients is 402 days (range, 28–728d).

Side-effects

Toxicity was graded according to ECOG criteria [8]. The most commonly encountered side-effects attributable to CAF were leukopenia, thrombocytopenia, nausea and vomiting, mucositis and alopecia. Hematologic toxicity was documented in 15 patients, life-threatening (Grade 4) toxicity occurred in one patient only. Nausea and vomiting occurred in 14 patients, severe vomiting occurred in one patient only. Side-effects attributable to buserelin were hot flushes and mild headaches. Hot flushes occurred in 11 patients, moderate in three and severe in eight patients. Four patients complained of headaches.

Of the 22 evaluable patients 17 were still menstruating regularly when entered on study. Five had had hysterectomies with ovaries intact but were still premenopausal as judged by pre-study serum estradiol, FSH and LH. Amenorrhea occurred in 13/17 women after a median of 60 days on treatment (range, 30–390 days). There was no significant correlation between the duration of treatment before the amenorrhea occurred and the age of the patients ($P = 0.154$). After 3 months on treatment the mean serum estradiol baseline values of 290 pmol/l (normal premenopausal values 37–1376), decreased to a mean of 32 pmol/l and remained at postmenopausal levels (0–50) while patients were on study (see Fig. 1). Mean FSH baseline values were 24 IU/l (normal premenopausal values 4–48) and mean LH baseline values were 39.5 IU/l (normal premenopausal values 1–115). Mean FSH and LH values are shown in Fig. 2.

Therapeutic results

ECOG response criteria were used. Responses were documented in 18 of the 22 evaluable patients (82%). Complete remissions (CR) occurred in seven patients and partial remissions (PR) in 11 patients. The median time to treatment failure was 402 days. Ten patients are still on study at a median of 496 days (range, 372–666 days). Patient characteristics and responses are shown in Table 1.

DISCUSSION

The response rate of 82% documented in this pilot study is comparable to the results reported in a large cooperative study where 131 premenopausal women with metastatic breast cancer were treated with CAF with or without oophorectomy. In the 131 patients studied by ECOG the CR plus PR

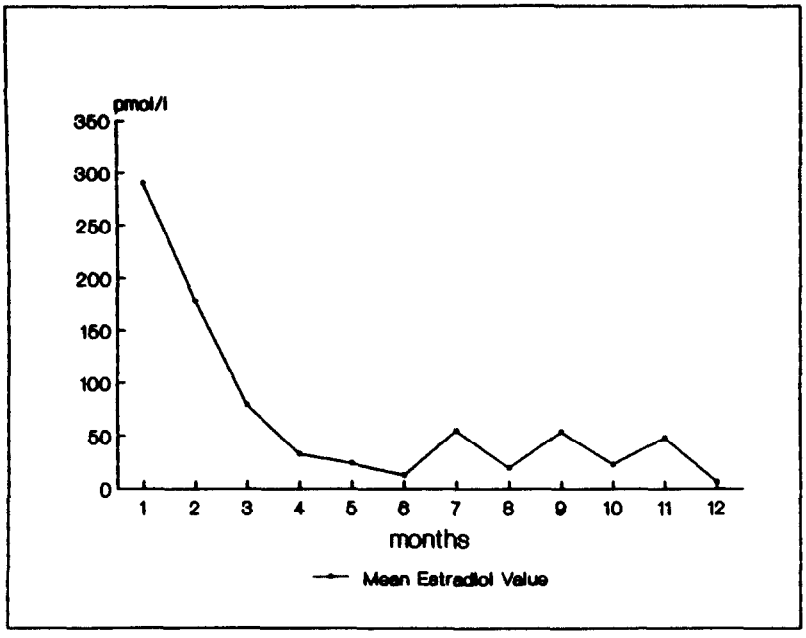

Fig. 1. Mean serum estradiol values in patients on CAF and nasal buserelin.

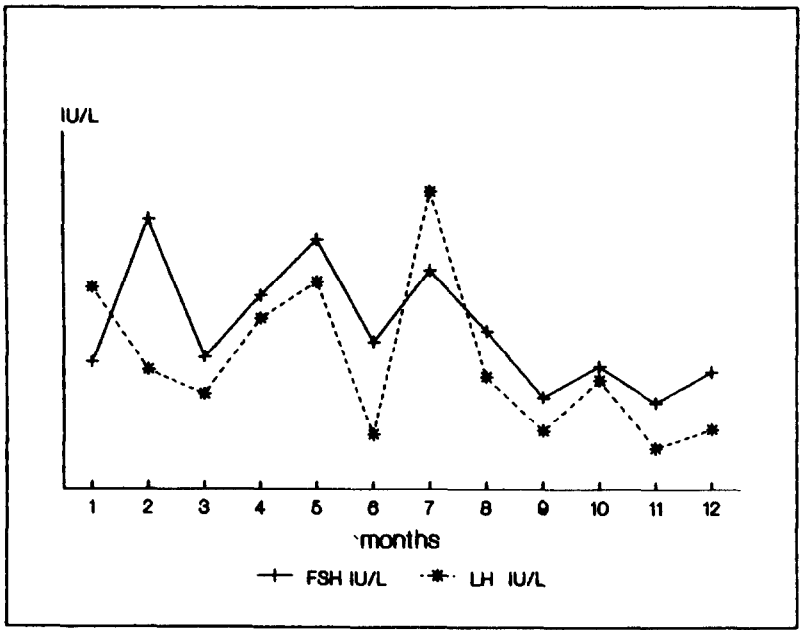

Fig. 2. Mean serum FSH and LH values in patients on CAF and nasal buserelin.

rate was 84% in those who received oophorectomy plus CAF, 76% in those who received CAF, and 68% in patients with ER-negative disease who were directly assigned to CAF [4]. In the study reported here the addition of buserelin to CAF did not increase the toxicities normally encountered with CAF alone; life-threatening hematologic toxicity occurred in one patient only. Side-effects ascribed to buserelin were hot flushes (in 50% of patients on the study) and mild headaches (in 18% of patients). These side-effects were mild to moderate and it was not necessary to decrease or stop treatment because of hot flushes or headaches.

Ovarian ablation remains an important therapeutic maneuver in the management of premenopausal women with advanced breast cancer. The availability of a form of medical oophorectomy would be a useful addition to the oncologist's armamentarium. Experimental studies in animals have shown that supraphysiological doses of gonadotrophin releasing hormone analogs (GnRHA) result, after a period of pituitary stimulation in desensitization of the gonadotrophs with consequent down-regulation of follicle stimulating hormone (FSH) and luteinizing hormone (LH) synthesis [9]. In males GnRHA administration inhibits

Table 1. Patient characteristics and response

Age	PS	Disease sites*	Hormone receptors ER	PGR	Prior adjuvant treatment	Response†	Duration on study (days)
50	0	N	+	+	None	CR	728
45	1	NS	−		CMFP	CR	259
37	1	N	+	−	None	CR	>666
37	1	L	Not done		CMFPT	CR	613
43	1	MNC	−	+	None	CR	100
40	0	N	−	−	None	CR	299
35	0	MN	+	−	None	CR	>473
32	1	B	Not done		None	PR	>534
57	0	B	+	+	None	PR	>416
47	1	BH	Not done		CMFPT	PR	265
42	1	BL	Not done		None	PR	>654
37	1	MBHS	Not done		None	PR	140
45	1	NB	+	+	CMFT	PR	>514
40	2	B	Not done		CMFPT	PR	326
50	1	BLP	+	+	CMFPT	PR	>493
46	0	M	+	+	None	PR	>484
37	0	NM	Not done		None	PR	389
39	1	BL	−	−	None	PR	>499
35	0	HB	+		None	NC	>372
46	1	HP	−	+	None	PD	60
47	2	SP	+	+	CMFPT	PD	28
40	3	HLBSM	−	−	None	PD	60
39	1	MBN	Not done		None	NE	10
37	1	BH	Not done		None	NE	7

*Disease sites: M = breast, L = lung, P = pleura, H = liver, B = bone, C = CNS, S = soft tissue and/or skin, N = lymph nodes.

†Response (ECOG criteria): CR = complete remission, PR = partial remission, NC = stable disease, PD = progression, NE = not evaluable.

FSH and LH production [10, 11]. The effect of intranasal administration of the GnRHA, buserelin, on FSH and LH in women appears to be less predictable as can be seen from our results. However, of the 17 menstruating women in our pilot study, 13 developed amenorrhea and all patients had a decrease of serum estradiol values from baseline premenopausal levels to postmenopausal levels. Klijn and de Jong [7], reporting on four premenopausal patients treated with nasal buserelin only for metastatic breast cancer, noted that all four patients became anovulatory; however, FSH and LH fell but rose again and very low LH levels were not reached during their brief observation period. While the intranasal route is an easy and non-invasive way to administer the agent the availability of depo-formulations for subcutaneous implants can be expected to have a more consistent effect on the secretion of gonadotrophins.

The study reported here has shown that (a) buserelin is well tolerated when given with CAF, (b) therapeutic results in the premenopausal women with advanced breast cancer, treated in this study, were not adversely affected by the addition of buserelin to CAF, (c) serum estradiol levels of all patients decreased to, and remained at, postmenopausal levels while on buserelin.

We conclude that further studies assessing the effect of the GnRHA, buserelin, in the management of premenopausal women with breast cancer are indicated.

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