# Combined Treatment with Buserelin and Cyproterone Acetate in Metastatic Male Breast Cancer

*Massimo Lopez, M.D.,* Maurilio Natali, M.D.,† Luigi Di Lauro, M.D.,* Patrizia Vici, M.D.,* Francesco Pignatti, M.S.,* and Silvia Carpano, M.D.**

***Background.*** **Male breast cancer (MBC) is considered an androgen-dependent tumor, and as in prostatic cancer, responses have been reported with use of antiandrogens or gonadotropin-releasing hormone analogs. Thus, it is reasonable to postulate that better results could be achieved by combining these two agents.**

***Methods.*** **Eleven men with recurrent or progressive carcinoma of the breast have been treated with buserelin 1500 μg subcutaneously daily in the first week and 600 μg daily subsequently and cyproterone acetate (CPA) 100 mg twice a day orally starting 24 hours before the first dose of buserelin.**

***Results.*** **Objective responses have been observed in seven patients with a median duration of 11.5 months (range, 9–24+ months). Responses were not correlated to the dominant site of disease. Three patients had stable disease lasting 5 months. Median survival was 18.5 months. Side effects primarily were decrease or loss of libido, impotence, and hot flushes.**

***Conclusions.*** **Total androgen blockade with buserelin and CPA seems effective in the treatment of patients with advanced cancer of the male breast, but its superiority over standard androgen suppression remains to be demonstrated. *Cancer* 1993; 72: 502–5.**

**Key words: male breast cancer, hormonal treatment, cyproterone acetate, buserelin.**

It is well recognized that hormonal therapy plays an important role in the management of disseminated male breast cancer (MBC). Although for many years orchiectomy has been considered the best primary treatment, with response rates of 31–67%,[1–3] an increasing body of evidence suggests that several alternatives to this unpopular ablative procedure can be offered to patients with this disease. High response rates with low morbidity have been reported with a variety of hormonal agents, such as tamoxifen, cyproterone acetate (CPA), and medroxyprogesterone acetate.[4]

The identification of the structure of gonadotropin-releasing hormone (GnRH) and its synthesis, along with the development of potent and long-acting GnRH agonist analogs (GnRH-A), has resulted in new approaches to the treatment of endocrine-related tumors.[5] Chronic administration of GnRH-A produces paradoxical inhibition of the pituitary gonadal axis, which results in a marked decrease in serum gonadotropin levels with subsequent chemical castration that has been of value in controlling the growth of prostate cancer[6] and female breast cancer.[7] However, during the first week of therapy, there is an increase in gonadotropin and androgen levels, which in some patients is associated with a clinical worsening of the disease.[8] Attempts to avoid this increase with the use of estrogens have not been entirely successful,[9] whereas the use of antiandrogens has been reported to be more efficient in preventing disease flare.[10] In addition, the combination of a pure antiandrogen with a GnRH-A has been claimed to yield remarkable results in patients with prostate cancer caused by simultaneous neutralization of testicular and adrenal androgens.[10] Thus, it was reasonable to anticipate similar results in patients with MBC, which is an androgen-dependent tumor.

We report our preliminary experience with the GnRH-A buserelin in combination with the steroidal antiandrogen CPA in the treatment of metastatic MBC. The choice of CPA, instead of a pure antiandrogen, was dictated by its activity as single agent in MBC[11] and by its antigonadotropic properties,[12] which may result in

From the *Division of Medical Oncology II, Regina Elena Institute for Cancer Research, Rome; and the †Oncologic Center, G. Porfiri, Latina, Italy.

Address for reprints: Massimo Lopez, M.D., Istituto Regina Elena per lo Studio e la Cura dei Tumori, Viale Regina Elena 291, 00161 Rome, Italy.

Accepted for publication March 9, 1993.

**Table 1. Patient Characteristics and Response to Therapy**

| Patient no. | Age (yr) | Primary tumor status | Disease-free interval (mo) | Receptor status | Previous treatment of metastases and response | Metastatic site(s) | Performance status (WHO) | Re-sponse | Duration of response (mo) | Survival (mo) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 47 | pT1 Nx M1 | 0 | ER− PgR− | CMF (NC 4 mo) | Bone | 2 | PD | — | 9 |
| 2 | 55 | pT2 N1 M0 | 18 | ER+ PgR+ | FEC (PD 3 mo) | Liver, soft tissue | 1 | CR | 12 | 18 |
| 3 | 62 | pT4 N2 M0 | 14 | NE | CMF (Adj) | Lung, soft tissue | 1 | NC | 6 | 17 |
| 4 | 70 | pTx N0 M0 | 21 | ER+ PgR+ | FEC (NC 6 mo) | Bone | 1 | PR | 12 | 46 |
| 5 | 46 | pT2 N0 M0 | 53 | NE | RT (Adj) | Bone | 2 | NC | 5 | 43+ |
| 6 | 63 | pT4 N1 M0 | 63 | ER+ PgR+ | RT (Adj)<br>TAM (PR 8 mo) | Bone, soft tissue | 2 | PR | 11 | 42+ |
| 7 | 52 | pT2 N1 M1 | 0 | ER+ PgR+ | CMF (PR 8 mo) | Bone, lung, soft tissue | 2 | PR | 9 | 20 |
| 8 | 47 | pT2 Nx M0 | 12 | ER− PgR− | — | Bone | 3 | NC | 5 | 13 |
| 9 | 59 | pT2 N1 M0 | 26 | ER− PgR+ | — | Lung | 1 | CR | 24+ | 24+ |
| 10 | 62 | pT1 N0 M0 | 36 | NE | MPA (NC 5 mo) | Lung, bone | 3 | PR | 15+ | 15+ |
| 11 | 64 | pT1 N1 M0 | 16 | ER+ PgR+ | TAM (PR 10 mo) | Bone, soft tissue | 1 | PR | 10+ | 10+ |

ER: estrogen receptors; PgR: progesterone receptors; NE: not evaluated; Adj: adjuvant; CMF: cyclophosphamide, methotrexate, 5-fluorouracil; RT: radiation therapy; TAM: tamoxifen; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; MPA: medroxyprogesterone acetate; CR: complete response; PR: partial response; NC: no change; PD: progressive disease.

an additive effect when administered simultaneously with a GnRH analog.

## Patients and Methods

Since April 1986, 11 men with recurrent or progressive carcinoma of the breast were admitted to this study. The clinical characteristics of these patients are reported in Table 1. All patients had histologically confirmed diagnosis of breast carcinoma, measurable or evaluable lesions, and a life expectancy of at least 2 months. All but two patients were pretreated with chemotherapy or additive hormonal therapy or radiation therapy. None had undergone anti-cancer therapy during the last 4 weeks.

Pretreatment evaluation included medical history and physical examination, biochemical profile, electrocardiogram, carcinoembryonic antigen, chest radiograph, skeletal survey, liver ultrasound scan, or abdominal computed tomography. Additional studies were performed if clinically indicated. Serum levels of luteinizing hormone, follicle-stimulating hormone, estradiol, testosterone, and prolactin were obtained basally daily during the first week, weekly during the first month, and monthly thereafter. Oral informed consent was obtained from all patients.

Buserelin [D-Ser ($Bu^t$)$^6$-LHRH (1–9)-ethylamide] was administered at a dose of 1500 μg daily (in three divided doses) during the first week. The daily dose was then reduced to 600 μg (in three divided doses). All patients received the drug subcutaneously to provide more reliable and higher amounts by avoiding the erratic absorption of the nasal spray route.

Cyproterone acetate, 100 mg twice a day, was given orally starting 24 hours before the first dose of buserelin.

Treatment was continued until tumor progression. Objective response was evaluated according to the criteria of the World Health Organization.[13] Duration of response was dated from the first day of treatment to date of progression. Survival from the initiation of treatment to death was calculated by the actuarial method of Kaplan–Meier.[14]

## Results

As outlined in Table 1, objective responses were achieved in seven patients for a median duration of 11.5 months (range, 9–24+ months). Responses were observed regardless of dominant site of disease. One patient experienced complete disappearance of lung metastases, and one complete disappearance of liver and soft tissue metastases. Three patients had stable disease with a median duration of 5 months. These patients had a subjective remission, as manifested by significant pain relief or improvement in performance status. Except for estrogen receptor status, no correlation could be identified between patient pretreatment characteristics and likelihood of response to the combined administration of buserelin and CPA. The median duration of survival was 18.5 months. Hormonal changes during treatment were determined in eight patients. During the first few days (Fig. 1), an initial phase of luteinizing hormone and follicle-stimulating hormone stimulation occurred, which soon disappeared. After 2–4 weeks of continuous daily therapy, the gonadotro-

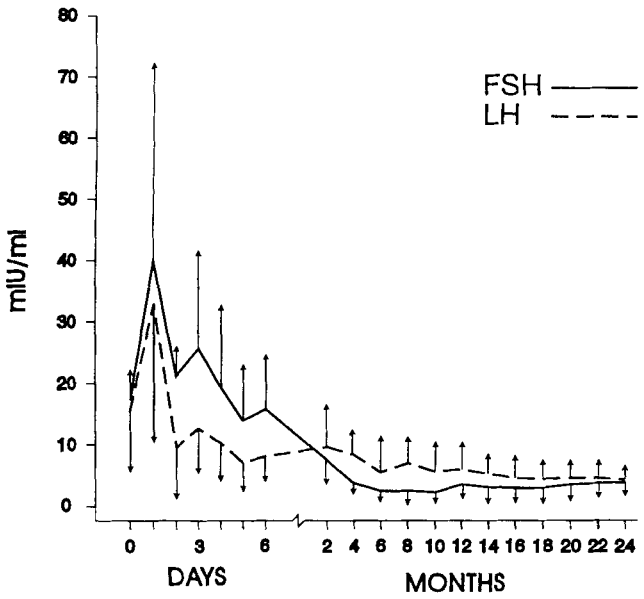


Figure 1. Plasma follicle-stimulating hormone and luteinizing hormone levels in eight patients receiving CPA plus buserelin. Results as mean and SEM.

pins were suppressed. Plasma testosterone concentrations (Fig. 2) followed a similar pattern, with suppression to castration levels (less than 1 ng/ml) in all patients, and remained low throughout treatment. Other hormonal changes included a significant decrease in serum estradiol levels to 29.8% ± 10.2% of basal (Fig. 2) and a prolactin increase by 265% ± 54% from basal values.

Treatment with CPA and buserelin was well tolerated. Decrease or loss of libido and sexual impotence were universal. Five patients experienced mild hot flushes, and one had gynecomastia. Disease flare never occurred. Hepatic dysfunctions in relation to CPA treatment were not observed.

## Discussion

With the exception of some anecdotal reports,[15] the growth of MBC generally has been stimulated by androgens, and the main principle in the treatment of advanced disease has been to effectively lower circulating levels of these hormones. Orchiectomy, although effective, has limited application for cultural and psychologic reasons. Additive hormonal therapy with estrogens or progestational agents may have a role, but side effects can be troublesome. Several new agents block hormonal action by a number of different mechanisms. Tamoxifen is the most thoroughly studied, with a 50% response rate in a cumulative series of 96 patients.[16] Antiandrogens[11] and buserelin[17,18] have been reported effective in inducing responses in advanced MBC when used singly. With the aim to improve treatment results by creating an androgen-free milieu, these agents were used in combination, and a remarkable improvement in progression-free survival and overall survival was reported in patients with metastatic prostatic cancer.[10]

In this study, the combination of CPA and buserelin produced therapeutic responses in 7 of 11 patients with advanced MBC for an overall response rate of 64%. Three other patients experienced stable disease that lasted 5 months. Others have reported similar results with a GnRH-A combined with flutamide. Doberauer et al.[18] achieved four partial responses in five patients treated with buserelin and flutamide, whereas Labrie et al.[19] observed a complete response with gona-

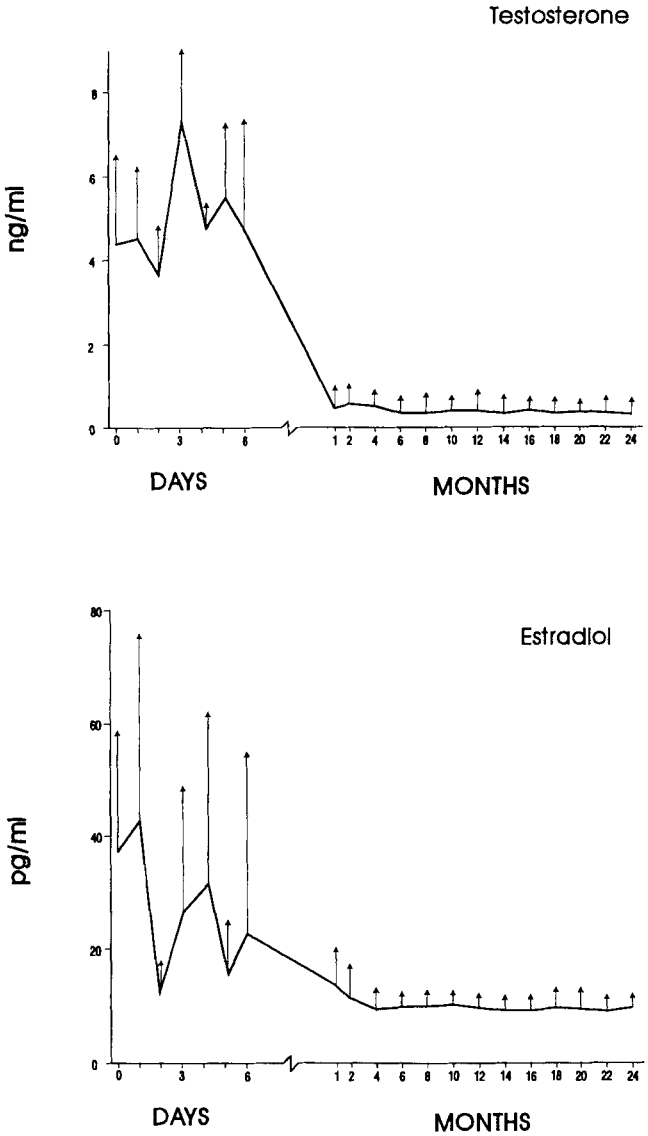


Figure 2. Plasma testosterone and estradiol levels in eight patients receiving CPA plus buserelin. Results as mean and SEM.

dorelin and flutamide in a patient with multiple bone metastases.

We did not observe correlation between patient age, performance status, disease-free interval, metastatic sites, prior therapy, and response to therapy. The combination treatment was highly effective in decreasing serum testosterone concentrations, but this did not translate into a beneficial effect for all patients, and the therapeutic responses were not related to the grade of suppression. This raises the question of whether or not there is an advantage to instituting a total androgen ablation. For this purpose, comparing the results of this study with those obtained in 14 patients treated in a previous trial with CPA alone can be of value. The patient populations were similar, and in both trials the prognostic factors were well balanced. Although in the current study, testosterone was suppressed more than in the previous one (7.4% ± 4.1% versus 37.6% ± 28.9% of basal), the response rate (64% versus 57%), duration of response (11.5 months versus 8 months) and median survival (18.5 months versus 16 months) were not significantly different, although there was a trend in favor of the combined treatment. The small number of patients in each trial and the use of historical control preclude any firm conclusions about the merits of total androgen blockade, but it is noteworthy that similar conclusions can be drawn when large series of prostatic cancer patients are considered.[20] It is difficult to establish whether MBC is constituted by cells variably sensitive to androgens or by androgen-dependent and androgen-independent cells. However, this latter hypothesis seems more realistic when the variety of hormonal manipulations effective in metastatic MBC is considered.[4]

The flare phenomenon described in some patients during the initial phase of GnRH-A monotherapy[18] was not observed in our patients. This probably could be avoided by the addition of CPA. Other side effects were well tolerated by all patients.

In conclusion, although androgen suppression with CPA and buserelin appears to be effective in the care of patients with advanced MBC, the value of synchronous, rather than metachronous, ablation of adrenal androgens remains unknown. Given the small likelihood of a randomized trial, it is important to gather additional information from future careful studied series of patients.

## References


1. Meyskens FL, Tormey DC, Neifeld JP. Male breast cancer: a review. *Cancer Treat Rev* 1976; 3:83–93.
2. Everson RB, Lippman ME, Thompson EB, McGuire WL, Whittliff JL, De Sombre ER, et al. Clinical correlations of steroid receptors and male breast cancer. *Cancer Res* 1980; 40:991–7.
3. Kraybill WG, Kaufman R, Kinne D. Treatment of advanced male breast cancer. *Cancer* 1981; 47:2185–9.
4. Lopez M, Di Lauro L, Lazzaro B, Papaldo P. Hormonal treatment of disseminated male breast cancer. *Oncology* 1985; 42:345–9.
5. Schally AV, Comaru-Schally AM, Redding TW. Antitumor effects of analogues of hypotalamic hormones in endocrine-dependent cancers. *Proc Soc Exp Biol Med* 1984; 175:259–81.
6. Leuprolide Study Group. Leuprolide versus dihethylstilbestrol for metastatic prostate cancer. *N Engl J Med* 1984; 311:1281–6.
7. Klijn JGM, De Jong FH. Treatment with a luteinizing hormone-releasing hormone analogue (buserelin) in premenopausal patients with metastatic breast cancer. *Lancet* 1982; 2:1213–6.
8. Parmar H, Lightman SL, Allen L, Phillips RH, Edwards L, Schally AV. Randomized controlled study of orchiectomy vs long-acting D-TRP-6 LHRH microcapsules in advanced prostatic carcinoma. *Lancet* 1985; 2:1201–5.
9. Stien BS, Smith JA. DES lead-in to use of luteinizing hormone releasing hormone analogs in the treatment of metastatic carcinoma of the prostate. *Urology* 1985; 25:350–3.
10. Labrie F, Dupont A, Belanger A, Emond J, Monfette G. Simultaneous administration of pure androgens: a combination necessary for the use of luteinizing hormone-releasing hormone agonist in the treatment of prostate cancer. *Proc Natl Acad Sci USA* 1984; 81:3861–3.
11. Lopez M. Cyproterone acetate in the treatment of metastatic cancer of the male breast. *Cancer* 1985; 55:2334–6.
12. Jacobi GH, Altwein JE, Kurth KH, Basting R, Hohenfellner R. Treatment of advanced prostatic cancer with parenteral cyproterone acetate: a Phase III randomised trial. *Br J Urol* 1980; 52:208–15.
13. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; 47:207–14.
14. Kaplan EL, Meyer P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc* 1958; 53:457–81.
15. Horn Y, Roof B. Male breast cancer: two cases with objective regressions from calusterone (7$\alpha$,17$\beta$-dimethyltestosterone) after failure of orchiectomy. *Oncology* 1976; 33:188–91.
16. Kinne DW, Hakes TB. Male breast cancer. In: Harris JR, Hellman S, Henderson IC, Kinne DW, editors. Breast diseases. 2nd ed. Philadelphia: JB Lippincott, 1991:782–90.
17. Vorobiof DA, Falkson G. Nasally administered buserelin inducing complete remission of lung metastases in male breast cancer. *Cancer* 1987; 59:688–9.
18. Doberauer C, Niederle N, Schmidt CG. Advanced male breast cancer treatment with the LH-RH analogue buserelin alone or in combination with the antiandrogen flutamide. *Cancer* 1988; 62:474–8.
19. Labrie F, Dupont A, Belanger A, Lacourciere Y, Beland L, Cusan L, et al. Complete response to combination therapy with an LHRH agonist and flutamide in metastatic male breast cancer: a case report. *Clin Invest Med* 1990; 13:275–8.
20. Iversen P, Christensen MG, Friis E, Hornbol P, Hvidt V, Iversen HG, et al. A Phase III trial of zoladex and flutamide versus orchiectomy in the treatment of patients with advanced carcinoma of the prostate. *Cancer* 1990; 66:1058–66.