Cancer Chemother Pharmacol (1988) 22: 172–174

Cancer Chemotherapy and Pharmacology


# Estramustine phosphate (estracyt) following androgens in men with refractory stage D2 prostate cancer*

**Francesco Boccardo[1], Andrea Decensi[1], Domenico Guarneri[1], Giuseppe Martorana[2], Claudio Giberti[2], and Luciano Giuliani[2]**

[1] Department of Clinical Oncology, National Cancer Institute, Genova, Italy
[2] Department of Urology, University of Genova, Italy

**Summary.** Twenty-two orchiectomized men with progressive stage D2 prostate cancer were treated with a 3-week cycle of estramustine phosphate (EMP: from day 3 to day 21) and androgen priming (from day 1 to day 4). A partial response according to the NPCP-USA criteria was shown in 4 of 20 evaluable patients. Median progression-free survival of all patients was 24 weeks (range, 4–48) and median survival, 42 weeks (range, 4–112). Although in two cases treatment had to be stopped due to a marked increase in bone pain, no life-threatening side effects were observed. The androgen sensitivity of tumors was supported by the occurrence of increase in prostatic phosphatase and in bone pain in most patients. In this group of patients, androgen priming did not seem to potentiate the effectiveness of EMP, our results being comparable to those previously reported using EMP alone.

## Introduction

Estramustine phosphate (Estracyt, EMP) is a molecule combining estradiol and nornitrogen mustard by a carbamate link. Despite the extensive use of this drug, its mechanism of action has not been completely elucidated. The lack of macromolecular alkylation, together with the observed antimitotic effects in vitro, imply a cytotoxic mechanism of action distinct from either of its constituent components [17].

Recent studies have shown that estramustine and estromustine, the active metabolites of EMP, are taken up in the ventral prostate gland of the rat and bound to a major protein distinct from the steroid receptors, which is called estramustine-binding protein (EMBP) [10]. A protein with similar properties has recently been found in humans, both in benign prostatic hyperplasia and in carcinomatous prostate [5]. Therefore, the uptake and action of EMP in the cancerous prostate tissue might depend on the presence of this protein [9]. Studies on rats have shown that EMBP is an androgen-dependent protein, i.e., its level decreases following castration or estrogen treatment and precastration levels are restored after the inoculation of androgens [5, 14]. This might partly explain the decrease in therapeutic activity reported for EMP in previously treated patients [4, 7], as compared to that in nontreated patients [2, 3, 7].

In view of these considerations, it would be appropriate to precede treatment with EMP by a period of androgen administration to increase the concentration of EMBP [9], especially in patients relapsing after orchiectomy. Moreover, the androgen treatment could stimulate tumor proliferation in prostate cells, as has been shown in vitro [1] and in vivo [6, 12] in rats, thus rendering such cells more sensitive to cytotoxic drugs [11]. In particular, the temporal pattern of the proliferative response has been shown to occur 72 h after androgen administration [6, 8, 12]. Clinical trials in advanced prostate cancer have recently been reported, in which chemotherapy with androgen priming was used [13, 16].

The purpose of this study was to investigate the feasibility and the possible effectiveness of a sequential combination of fluoxymesterone (Halotestin, F), a synthetic androgen, and EMP in orchiectomized patients with progressive stage D2 prostate cancer.

## Materials and methods

Between January 1984 and December 1985, 22 patients with histologically proven carcinoma of the prostate were entered into the study. Patient characteristics are summarized in Table 1. Eligibility criteria included an adequate trial of previous hormonal therapy, namely, orchiectomy, an expected survival of more than 3 months, and/or a performance status of $\leq 3$ according to the WHO criteria. Patients who had an additional neoplasm, radiation therapy to the only site of evaluable disease, or CNS metastases were excluded, as were patients with significant co-morbid conditions that could preclude the correct use of treatment. All patients underwent neurological examination before entry in order to rule out spinal cord compression symptoms. Informed consent meeting all institutional regulations was obtained prior to treatment. Treatment consisted of a 3-week cycle including oral F, 5 mg b.i.d. on days 1–4, followed by oral EMP, 280 mg (2 tablets) t.i.d. on days 3–21.

Patients who developed a disease flare while on F were kept on the drug unless the pain was severe and could not be controlled by analgesics. A general clinical evaluation was carried out every 3 weeks. Hemogram and blood chemistry tests were checked every 6 weeks. Prostatic acid

* This study was partially supported by a grant of the Italian National Research Council, Special Project "Oncologia", contract number 85.02188.44
*Offprint requests to:* Francesco Boccardo, National Cancer Institute, Viale Benedetto XV, 10, I-16132 Genova, Italy

**Table 1.** Patient characteristics

| | |
|---|---|
| Median age | 69 (58–79) |
| Median performance status | 1 (0– 3) |
| Median time to progression, following orchiectomy (months) | 14 (9–24) |
| Histological grade (Gaeta): | |
| G1 | 2 |
| G2 | 6 |
| G3 | 9 |
| G4 | 4 |
| GX | 1 |
| Prior therapy: | |
| Orchiectomy | 11 |
| Orchiectomy + cyproterone acetate | 8 |
| Orchiectomy + estrogens | 3 |
| Metastatic sites: | |
| Bone | 22 |
| Lymph nodes | 8 |
| Lung | 4 |
| Adrenal | 1 |

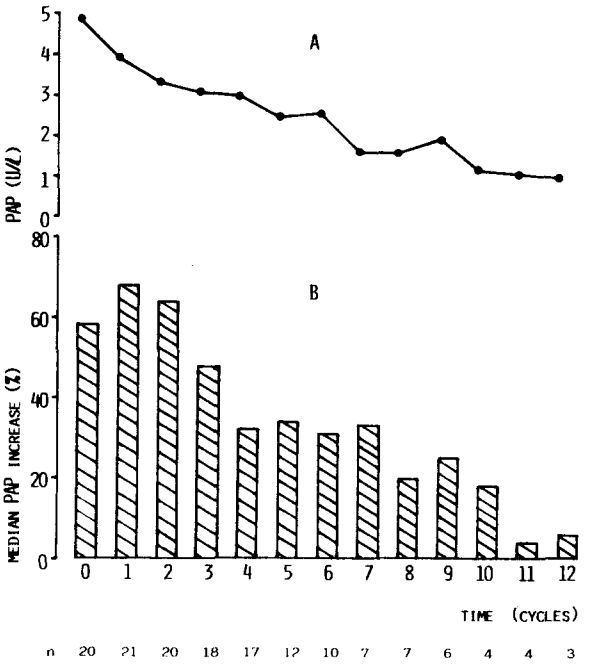


**Fig. 1.** *A* Median PAP levels before each androgen administration. *B* Median percentage of PAP increment following androgen administration. Number of patients is shown below the horizontal axis. Normal PAP range = 0–4 IU/l

phosphatase (PAP) was repeated twice every cycle on days 21 and 4, i.e., just before and at the end of androgen administration. PAP levels were estimated by RIA in a central laboratory. Skeletal X-rays, bone scans, prostatic ultrasonography, chest X-rays, and other instrumental exams, if needed, were repeated at 12-week intervals or earlier to document disease progression. Assessments of response were made according to the National Prostatic Cancer Project USA criteria [15]. Duration of survival and progression-free survival were calculated from the day treatment began until failure or the last day of contact.

## Results

Two patients were not evaluable for response: one died of a stroke after 4 weeks, and the other refused treatment after 6 weeks because of the inability to attend a proper follow-up plan.

Thus, following 12 weeks of treatment, 20 patients were fully evaluable for response: four had a partial response, eight were stable, and eight progressed. Of the four responders, two had a reduction of 50% in the number of increased uptake areas on the bone scan, while the other two had a 50% decrease in the prostate tumor and pelvic limph node size, respectively, documented by prostatic ultrasonography and pelvic CAT scan. In all these patients, PAP levels returned to normal values and the other sites of the disease remained stable. These four patients were previously treated with orchiectomy alone. Median progression-free survival in all patients studied, including those not considered for assessment of response, was 24 weeks (range, 4–48) and median survival was 42 weeks (range, 4–112).

PAP behavior is shown in Fig. 1. A decrease in median PAP levels, assessed just before androgen administration was observed throughout the treatment course (Fig. 1 A). The median percentage increment in PAP levels following each administration of F is shown in Fig. 1 B; values progressively decreased from cycle 0 to cycle 12.

Patients experiencing partial response or stable disease also exhibited a subjective improvement with decreased bone pain; in three cases the use of analgesics was suspended after 3, 4, and 6 courses, respectively. The most common side effects related to treatment are summarized in Table 2.

**Table 2.** Toxicity

| | No. of patients |
|---|---|
| Bone pain increase during F: | |
| Mild | 3 |
| Moderate | 5 |
| Severe | 2 |
| Nausea | 10 |
| Vomiting | 2 |
| Anorexia | 6 |
| Diarrhea | 1 |
| Increase in transaminase levels | 2 |
| Thrombocitopenia (< 100.000/mm³) | 2 |
| Leukopenia ( <4.000/mm³) | 2 |
| Rash | 2 |
| Cramps | 2 |
| Edema of the extremities | 2 |
| Painful gynecomastia | 8* |

* Six patients previously on estrogens or cyproterone

In ten cases, an increase in bone pain after the administration of F was initially recorded. Pain was graded as severe in two patients, moderate in five, and mild in three. In all cases but two, these symptoms progressively decreased with time and no longer required an additive analgesic. No episode of spinal cord compression occurred during androgen treatment.

## Discussion

The rationale of our study was to obtain an enhanced sensitivity to EMP through both the priming action on EMBP and the recruitment of resting cells. Although we could not investigate these phenomena specifically, the increase in PAP levels as well as in symptoms following the administration of F may suggest that tumor stimulation was achieved, thus indicating that hormone-refractory prostate cancer is still sensitive to endocrine modulation. In this regard our findings are similar to those previously reported by other investigators using androgen priming in combination with chemotherapy [13, 16].

The progressive decrease in the degree of PAP increment as a result of androgen treatment may be related to either a reduction of tumor burden or the selection of hormone-insensitive clones that had occurred with time. However, both phenomena might be explained merely by the decrease in the number of patients still under study at the different observation times.

The toxicity of the therapeutic regimen used in our study was generally mild, despite one early death, which could not be completely unrelated to treatment. The amenability of the induced symptoms seems to indicate that this approach is feasible, provided that an accurate patient selection, and in particular a neurological examination, is made to exclude those patients at risk for spinal cord compression. The other side effects induced by EMP do not seem to be increased by androgen administration. However, it appears that this approach cannot potentiate the effectiveness of EMP alone. In fact, the results achieved by us are comparable to those previously reported by others using EMP alone in treating refractory prostate cancer [4, 7].

Manni et al. [13] have recently reported the results of a randomized trial comparing chemotherapy with chemotherapy plus androgen priming in previously orchiectomized patients with stage D prostatic cancer. The objective remission rate was comparable in both arms, although a trend in favor of the stimulation arm was evident when the analysis was restricted to only evaluable patients. However, the authors reported a shorter duration of response and survival in the stimulation arm than in the control arm. The lack of improvement in duration of response and survival was explained by the presence of a large fraction of hormone-insensitive cells in patients with tumors refractory to orchiectomy.

In our study, a relatively short duration of progression-free and overall survival was also observed. Moreover, a twofold or even higher increase in median PAP levels was observed in our series during the first four cycles. Therefore, it cannot be excluded that the periodic androgen treatment might have eventually stimulated the growth of tumor clones intrinsically resistant to EMP. A similar phenomenon could explain the detrimental effect previously observed by Manni et al. [13] using the combined approach. Which ever mechanisms might be involved, it does not seem that androgen priming serves any useful purpose in the management of advanced prostate cancer.

*Acknowledgements.* The authors wish to thank Dr. Imre Könyves (Helsingborg) for reviewing this manuscript.

## References

1. Alison MR, Wright NA (1981) Growth kinetics. In: Duncan W (ed) Recent results in cancer research. Prostate cancer. Springer Verlag, Berlin Heidelberg New York, p 29
2. Andersson L, Berlin T, Boman, J, Collste L, Edsmyr F, Esposti PL, Gustafsson H, Hedlund PO, Hultgren L, Leander G, Nordle O, Norlen H, Tillgard P (1980) Estramustine versus conventional estrogenic hormones in the initial treatment of highly or moderately differentiated prostatic carcinoma. A randomized study. Scand J Urol Nephrol (Suppl) 55: 143
3. Benson RC Jr, Gill GM (1986) Estramustine phosphate compared with diethylstilbestrol. Am J Clin Oncol 9 (4): 341
4. Benson RC, Wear JB, Gill GM (1979) Treatment of stage D hormone-resistant carcinoma of the prostate with estramustine phosphate. J Urol 121: 452
5. Bjork P, Forsgren B, Gustafsson JA, Hogborg B (1982) Partial characterization and "quantitation" of a human prostatic estramustine-binding protein. Cancer Res 42: 1935
6. Coffey DS, Shimazaki J, Williams-Ashman HG (1968) Polymerization of deoxyribonucleotides in relation to androgen-induced prostatic growth. Arch Biochem Biophys 124: 184
7. Edsmyr F, Andersson L, Könyves I (1982) Estramustine phosphate (estracyt): Experimental studies and clinical experience. In: Jacobi GH, Hohenfellner R (eds) Prostate cancer. Williams and Wilkins, Baltimore, London, p 253
8. English HF, Drago JR, Santen RJ (1985) Cellular response to androgen depletion and repletion in the rat ventral prostate: autoradiography and morphometric analysis. Prostate 7: 41
9. Forsgren B, Bjork P (1984) Specific binding of estramustine to prostatic proteins. Urology (Suppl) 23 (6): 34
10. Forsgren B, Gustafsson JA, Pousette A, Hogberg B (1979) Binding characteristics of a major protein in rat ventral prostate cytosol that interacts with estramustine, a nitrogen mustard derivative of 17 β-estradiol. Cancer Res 39: 5155
11. Grossman HB, Kleinert EL, Lesser ML, Herr HW, Whitmore WF Jr (1981) Androgen stimulated chemotherapy in the Dunning R-3327 prostatic adenocarcinoma. Urol Res 9: 237
12. Lesser B, Bruchovsky N (1973) The effect of testosterone and 5 alfa-dihydrotestosterone and adenosine 3',5'-monophosphate on cell proliferation and differentiation in rat prostate. Biochem Biophys Acta 308: 426
13. Manni A, Santen RJ, Boucher AE, Lipton A, Harvey H, Simmonds M, White-Hershey D, Gordon RA, Rohner TJ, Drago J, Wettlaufer J, Glode LM (1986) Androgen priming and response to chemotherapy in advanced prostatic cancer. J Urol 136: 1242
14. Pousette A, Bjork P, Carlstrom K, Forsgren B, Hogberg B, Gustafsson JA (1981) Influence of sex hormones on prostatic secretion protein, a major protein in rat prostate. Cancer Res 41: 688
15. Slack NH, Brady MF, Murphy GP and Investigators in National Prostatic Cancer Project (1984) A reexamination of the stable category for evaluating response in patients with advanced prostate cancer. Cancer 54: 564
16. Suarez AJ, Lamm DL, Radwin HM, Sarosdy M, Clark G, Osborne CK (1982) Androgen priming and cytotoxic chemotherapy in advanced prostatic cancer. Cancer Chemother Pharmacol 8: 261
17. Tew KD, Hartley B (1984) Cytotoxic properties of estramustine unrelated to alkylating and steroid constituents. Urology (Suppl) 23 (6): 28

Received August 12, 1987/Accepted March 3, 1988