# Prevention of the initial testosterone surge induced by a luteinizing hormone-releasing hormone analogue in prostate cancer patients : the endocrinological effects of pretreatment with chlormadinone acetate

Akihiro Yamamoto, Yoshiteru Sumiyoshi*, Noriaki Miyake**, Hideaki Yokozeki†, Hiro-omi Kanayama‡, and Susumu Kagawa‡

*Department of Urology, Kochi Takasu Hospital, Kochi, Japan; *Department of Urology, National Shikoku Cancer Center Hospital, Ehime, Japan; **Department of Urology, Yashima General Hospital, Kagawa, Japan ; †Department of Urology, Tokushima Municipal Hospital, Tokushima, Japan ; and ‡Department of Urology, The University of Tokushima School of Medicine, Tokushima, Japan*

**Abstract : We investigated the endocrinological effects of pretreatment with chlormadinone acetate (CMA) in preventing the initial testosterone surge induced by a luteinizing hormone-releasing hormone (LH-RH) analogue. A total of 25 patients with previously untreated prostate cancer were included in this study. The patients were randomly assigned to 2 treatment groups : Group 1 ; CMA therapy was begun 4 weeks before the initial LH-RH analogue injection. Group 2 ; CMA therapy was begun 2 weeks before the initial LH-RH analogue injection. After the initial LH-RH analogue injection, CMA was administered during this study. After LH-RH analogue application, the mean values of serum luteinizing hormone (LH) and testosterone increased in both groups on day 3. However, LH and testosterone levels remained beneath pretreatment values in both groups. The mean relative PSA levels did not significantly increased on day 3 and day 7 in both groups. Our results indicate that pretreatment with CMA for 2 weeks was sufficient to prevent the initial testosterone surge in the maximal androgen blockade which was associated with CMA. J. Med. Invest. 46 : 55-58, 1999**

***Key words*** **:** *Prostate cancer, Luteinizing hormone-releasing hormone analogue, Disease flare, Chlormadinone acetate*

## INTRODUCTION

The luteinizing hormone-releasing hormone (LH-RH) analogue induces a transient release of luteinizing hormone (LH) with a consecutive increase in testosterone, and this increase results in exacerbation of clinical signs and symptoms in some prostate cancer patients [1, 2]. Several studies have demonstrated that this disease flare can be effectively eliminated by the use of antiandrogens in combination with or before initiation of LH-RH analogue therapy [3-6]. However, the optimal duration of pretreatment is rather difficult to determine. We herein report the endocrinological effects of pretreatment with the steroidal antiandrogen, chlormadinone acetate (CMA ; 6-chloro-3,20-dioxo-4, 6-pregnadien-17-yl acetate, Teikoku Hormone MFG Co. Tokyo, Japan) for the prevention of this initial testosterone surge.

Received for publication November 17, 1998 ; accepted December 25, 1998.

Address correspondence and reprint requests to Dr. Akihiro Yamamoto, Department of Urology, Kochi Takasu Hospital, Takasu-shin-machi, Kochi 780-8122, Japan and Fax : +81-888-84-1892.

## PATIENTS AND METHODS

A total of 25 patients with previously untreated prostate cancer (stage B, C, D) proved by biopsy were included in this study. All patients gave informed

consent to participate in the study. The patients were assigned randomly to 2 treatment groups. Group 1 patients were treated with the depot LH-RH analogue (leuprorelin acetate 3.75 mg or goserelin 3.6 mg) plus CMA. CMA therapy was begun 4 weeks before the initial LH-RH analogue injection at a dosage of 100 mg/day orally. Group 2 patients were treated with the LH-RH analogue plus CMA at the same dosages used in group 1 with the exception that CMA therapy was begun 2 weeks before the initial LH-RH analogue injection. After the initial LH-RH analogue injection, CMA was administered to both groups.

Serum LH, testosterone, and prostate specific antigen (PSA) were measured in each patient before the initial CMA administration, and on days 0, 3, 7, and 28 of LH-RH analogue therapy. Serum LH (Spack-S LH kit, Daiichi Radioisotope Laboratories Ltd., Tokyo, Japan) and testosterone (Total Testosterone, Diagnostic Products Corporation, Los Angels, USA) levels were measured by radioimmunoassay. PSA assay was performed by the monoclonal Hybritech Tandem-R immuno-radiometric technique (Tandem-R PSA, Hybritech. Inc., San Diego, USA). Due to the wide variation of the initial values of serum PSA, we investigated the mean relative PSA levels. Relative values were expressed as a percentage of the initial value for each patient before therapy started, which was considered 100%.

Histologically, differentiation of adenocarcinoma was evaluated according to the criteria of the General Rules for Clinical and Pathological Studies on Prostatic Cancer [7]. Data are presented as means ±SD (standard deviation). For statistical analysis, the Wilcoxon one sample analysis, paired Wilcoxon test and Mann-Whitney U test were used and a P value below 0.05 was considered to indicate statistical significance.

## RESULTS

The characteristics of the patients are shown in table 1. There were no significant differences between the 2 treatment groups in the initial age, histopathological grade, clinical stage, serum LH, testosterone and PSA levels at the start of treatment.

The mean absolute values of serum LH and testosterone in both groups are shown in figures 1 and 2. Pretreatment with CMA decreased serum LH levels. Compared to day 0 (the initial injection

Table 1. Patient characteristics

| | Group 1 (n=12) | Group 2 (n=13) |
|---|---|---|
| Age (years) | 75.5±8.0 | 75.4±7.0 |
| Histopathological grade | | |
| Well | 4 | 2 |
| Moderate | 5 | 4 |
| Poor | 3 | 7 |
| Stage | | |
| B 1 | 2 | 3 |
| B 2 | 2 | 3 |
| C | 4 | 6 |
| D 2 | 4 | 1 |
| LH (mIU/ml) | 5.9±2.6 | 12.7±9.5 |
| Testosterone (ng/dl) | 422.2±152.7 | 528.2±173.7 |
| PSA (ng/ml) | 129.0±176.8 | 60.0±63.7 |

Values are means±S.D.

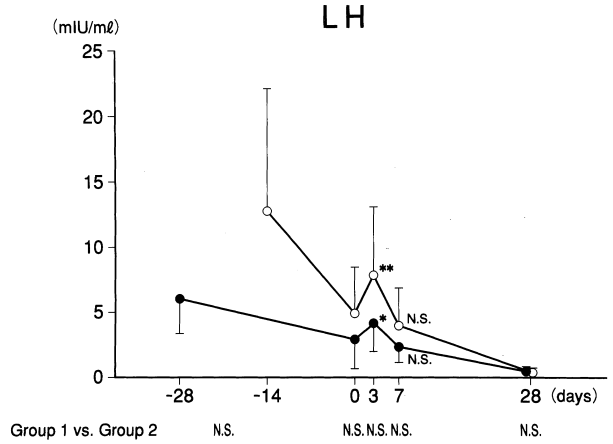


Fig.1. Effects of CMA pretreatment on serum LH in prostate cancer patients. LH-RH analogue was administered on day 0. Values are mean±S.D.; Closed circle, Group 1, n=12; Open circle, Group 2, n=13. *p<0.05, **p<0.01, ***p<0.001 vs. day 0.

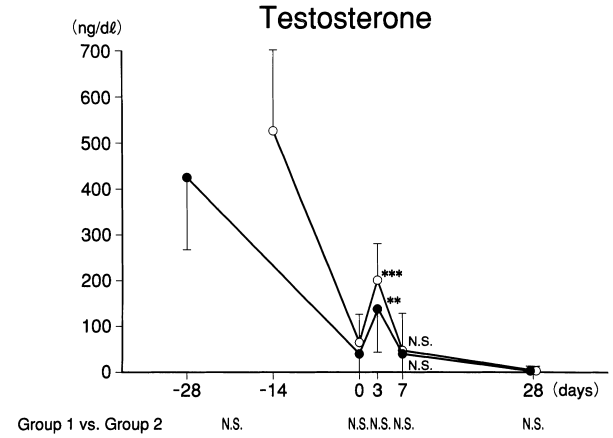


Fig. 2. Effects of CMA pretreatment on serum testosterone in prostate cancer patients. LH-RH analogue was administered on day 0. Values are mean±S.D.; Closed circle, Group 1, n=12; Open circle, Group 2, n=13. **p<0.01, ***p<0.001 vs. day 0.

of the LH-RH analogue), the serum LH levels were increased on day 3 (Group 1 ; 2.83±2.22 vs. 4.06 ±2.05 mIU/ml, Group 2 ; 4.92±3.61 vs. 7.95±5.23 mIU/ml), and then decreased. However, the serum LH levels on day 3 did not reach pretreatment levels in either group. There were no significant differences in serum LH levels between the groups on days 0, 3, 7, and 28. The serum testosterone levels showed a parallel decrease with LH until day 0, and reached castration levels below 100 ng/dl in both groups. Temporary increases were observed on day 3 (Group 1 ; 138.12±95.82 ng/dl, Group 2 ; 202.58±81.70 ng/dl), but did not reach pretreatment levels. On day 7, serum testosterone levels decreased to castration levels in both groups. There were no significant differences in serum testosterone levels between the groups on days 0, 3, 7, and 28.

The mean relative values of serum PSA are shown in figure 3. CMA pretreatment significantly reduced serum PSA. On day 0, the mean relative values of serum PSA in group 2 (45.31±24.76%) were higher than those in group 1 (24.92±11.89%). There were no significant differences among the groups on days 3, 7, and 28. In group 2, the mean relative values of serum PSA were significantly lower on day 3 (38.26 ±19.71%) and day 7 (35.25±19.62%) than on day 0 (45.31±24.76%). However, the mean relative PSA levels were not lower on day 3 (25.26±12.34%) or day 7 (27.68±12.31%) than on day 0 (24.92±11.89 %) in group 1. In 3 cases in group 1, the mean relative values of serum PSA decreased in a linear fashion after the initial injection of the LH-RH analogue, and all 3 cases exhibited well differentiated adenocarcinoma. In contrast, increases in the mean relative values of serum PSA on day 7 compared to days 0 or 3 were observed in 9 cases. The adenocarcinoma was well differentiated in 1 case, moderate in 5, and poor in 3. Increases in the mean relative values of serum PSA on day 7 were more frequently seen in the patients with high histopathological grade ($p<0.05$). There was no correlation between the change in mean relative values of serum PSA and the clinical stage.

No signs or symptoms of disease flare were observed in either group.

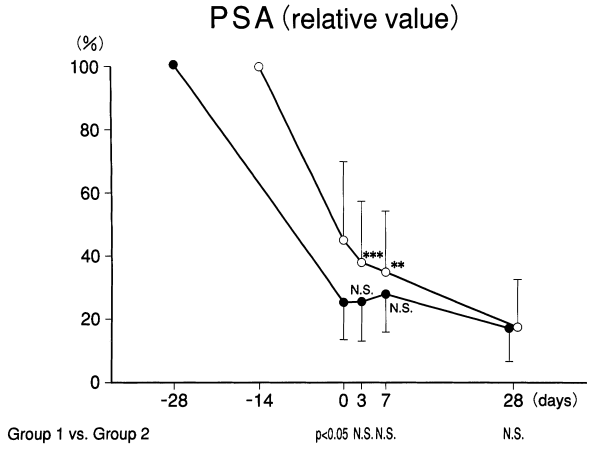


Fig. 3. Effects of CMA pretreatment on mean relative values of serum PSA in prostate cancer patients. LH-RH analogue was administered on day 0. Values are mean±S.D. ; Closed circle, Group 1, n=12 ; Open circle, Group 2, n=13. **p<0.01, ***p<0.001 vs. day 0.

## DISCUSSION

Since disease flare is considered to be due to the initial increase in serum testosterone, the use of antiandrogens in combination with or before initiation of a LH-RH analogue has been advocated. Labrie *et al.* [3] reported that the concomitant administration of the nonsteroidal antiandrogen, flutamide, completely eliminated the risk of disease flare. On the other hand, Schulze *et al*. [4] indicated that pretreatment with flutamide for only 1 day may not be sufficient to prevent tumor flare, and should begin 1 week before the LH-RH analogue injection. However, from an endocrinological viewpoint, the effects of nonsteroidal antiandrogens in preventing disease flare are rather difficult to determine due to their mode of action [6]. Pretreatment with the steroidal antiandrogen, cyproterone acetate, for 1 week prevented the LH-RH analogue induced testosterone surge and an initial increase in prostatic acid phosphatase beyond the pretreatment levels [4]. The administration of estramustine phosphate 560 mg daily for 3 weeks prior to goserelin acetate depot therapy was also considered sufficient to prevent tumor flare [6].

The steroidal antiandrogen CMA was reported to reduce serum testosterone levels and block the binding of androgens to androgen receptors in prostatic carcinoma tissue [8]. Nishimura *et al*. [9] reported that the plasma testosterone concentration decreased to levels of normal females after 4-6 weeks of CMA administration, but increased to an average level of 109 ng/dl after 8-10 weeks of CMA administration. Yoshida *et al*. [5] investigated the efficacy of 2-week and 4-week pretreatment with 100 mg/day CMA to prevent disease flare in patients with metastatic carcinoma of the prostate. Since serum PSA levels significantly increased in the 2-week pretreatment group but showed a linear

decrease in the 4-week pretreatment group, they concluded that the 4-week regimen was more effective than the 2-week regimen [5]. However, there are two major differences from our study. First, CMA was discontinued after the LH-RH analogue therapy in their study. Second, they investigated the efficacy in patients with metastatic carcinoma of the prostate.

In recent meta-analyses, maximal androgen blockade (MAB) continues to be debated, with advocates both for and against its efficacy [10, 11]. In the present study, CMA was continued after the LH-RH analogue therapy for the purpose of MAB. The serum LH and testosterone levels were increased on day 3 compared to day 0, but did not reach pretreatment levels in either group. The mean relative values of serum PSA were significantly lower on day 3 and day 7 than on day 0 in group 2. However, the mean relative PSA levels were not lower on days 3 or 7 than on day 0 in group 1, despite the longer pretreatment. These results suggest that pretreatment for 2 weeks is sufficient to prevent the initial testosterone surge in the MAB which is associated with CMA. PSA change induced by a transient testosterone increase may be different in each case, and it seems to be difficult to identify the correlation factor. However, as shown in our results the histopathological grade may contribute to the difference. A larger prospective trial is necessary to elucidate this factor.

## REFERENCES

1. Faure N, Lemay A, Laroche B, Robert G, Plante R, Jean C, Thabet M, Roy R, Fazekas ATA : Preliminary results on the clinical efficacy and safety of androgen inhibition by an LHRH agonist alone or combined with an antiandrogen in the treatment of prostatic carcinoma. Prostate 4 : 601-624, 1983
2. Kahan A, Delrieu F, Amor B, Chiche R, Steg A : Disease flare induced by D-Trp6-LHRH analogue in patients with metastatic prostatic cancer. Lancet 1 : 971-972, 1984
3. Labrie F, Dupont A, Belanger A, Lachance R : Flutamide eliminates the risk of disease flare in prostatic cancer patients treated with a luteinizing hormone-releasing hormone agonist. J Urol 138 : 804- 806, 1987
4. Schulze H, Senge T : Influence of different types of antiandrogens on luteinizing hormone-releasing hormone analogue-induced testosterone surge in patients with metastatic carcinoma of the prostate. J Urol 144 : 934-941, 1990
5. Yoshida K, Takeuchi S : Pretreatment with chlormadinone acetate eliminates testosterone surge induced by a luteinizing -hormone-releasing hormone analogue and the risk of disease flare in patients with metastatic carcinoma of the prostate. Eur Urol 27 : 187-191, 1995
6. Shimizu T, Shibata Y, Jinbo H, Satoh J, Yamanaka H : Estramustine phosphate for presrventing flare-up in luteinizing hormone-releasing hormone analogue depot therapy. Eur Urol 27 : 192-195, 1995
7. Japanese Urological Association and the Japanese Pathological Society : General Rules for Clinical Pathological Studies on Prostatic Cancer, ed 2. Kanehara Shuppan, Tokyo, 1992
8. Shida K : Fundamental and clinical study on anti-androgen-androgen dependency of prostatic tumors and clinical application of antiandrogens. Asian Med J 24 : 747-776, 1981
9. Nishimura R, Shida K : Antiandrogenic therapy for the treatment of early stage prostatic cancer. Prostate 1 (suppl) : 27-34, 1981
10. Prostate Cancer Trialists 'Collaborative Group : Maximum androgen blockade in advanced prostate cancer : an overview of 22 randomized trials with 3283 deaths in 5710 patients. Lancet 346 : 265-269, 1995
11. Caubet JF, Tosteson TD, Dong EW, Naylon EM, Whiting GW, Ernstoff MS, Ross SD : Maximum androgen blockade in advanced prostate cancer : A meta-analysis of published randomized controlled trials using nonsteroidal antiandrogens. Urology 49 : 71-78, 1997