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Chlormadinone acetate is effective for hot flush during androgen deprivation therapy

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Purpose: To investigate the clinical efficacy of low-dose chlormadinone acetate (CMA) in prostate cancer patients who suffer from hot flushes that is a major side effect of androgen deprivation therapy.

Methods: Our study included 32 prostate cancer patients who had severe hot flush after undergoing hormone therapy for more than 3 months. The average age of the patients was 72.5 years. In the beginning, patients received CMA at 100 mg orally per day. We defined the hot flush as disappeared, improved, or not improved. In patients with disappeared or improved symptoms, we decreased CMA dose to 50 mg per day, and after we reevaluated the effect, we decreased CMA dose to 25 mg per day. When hot flush appeared again at 25 mg per day, we returned the dose of CMA to 50 mg per day. In cases with no change for more than two months, we canceled the treatment of CMA.

Results: Hot flush disappeared in 17 patients, improved in 10 patients, and did not improve in 5 patients (reduction in 84% of hot flush patients). The median time to hot flush reduction was 1.16 months. The effect of CMA was maintained at 25 mg per day in 19 patients and at 50 mg per day in 8 patients. No patients had prostate-specific antigen failure in the treatment of CMA.

Conclusions: When hot flush appears during treatment with luteinizing hormone-releasing hormone agonist for prostate cancer, it seems that CMA can improve it immediately in most patients.

Keywords: Hormonal antineoplastic agents, Chlormadinone acetate, Hot flashes, Prostate neoplasms

INTRODUCTION

Hot flush is a major side effect of androgen deprivation therapy for prostate cancer patients. Up to 80% of patients undergoing treatment with gonadotropin-releasing hormone (GnRH) analogues report hot flushes, and up to 27% report hot flushes as being the most troublesome side effect of treatment [1]. Although the pathophysiology of hot flush is incompletely understood, a number of effective therapies are available for its management. For example, there are transdermal estrogen patch [2] and megestrol acetate [3] amongst hormonal treatment options, and clonidine [4], gabapentin [5], and selective serotonin reuptake inhibitor (SSRI) [6] amongst nonhormonal treatment options.

Chlormadinone acetate (CMA) is a steroidal antiandrogen similar to progesterone used in maximum androgen blockade (MAB) therapy as well as monotherapy for prostate cancer in Japan. We investigated the clinical efficacy of low-dose CMA in prostate cancer patients who suffer from hot flushes.

MATERIALS AND METHODS

Our study included 32 prostate cancer patients who had severe hot flush after undergoing hormone therapy for more

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Table 1. The characterisitics of the enrolled patients

Characterisitic	Value
Age (yr), average (range)	72.5 (59–85)
Serum PSA (ng/mL)	
<10	14
10–20	10
>20	8
Testosterone (ng/mL), average (range)	4.16 (2.1–8.7)
Clinical stage	
T1–T2N0M0	24
T3N0M0	6
N1M0	1
M1	1
Gleason score	
6	3
7	20
8	2
9	7
Purpose of use of LH-RHa	
Monotherapy	15
Combination with radiation	15
Salvage	2

PSA, prostate-specific antigen; LH-RHa, luteinizing hormone-releasing hormone agonist.

than 3 months (Table 1). In 30 patients who had been treated with only luteinizing hormone-releasing hormone (LH-RH), CMA was administered. In 2 patients who had been treated with MAB using bicalutamide (and whose cancer control was good), bicalutamide was changed to CMA. The average age of the patients was 72.5 years. The mean of prostate-specific antigen (PSA) before LH-RH agonist treatment was 35.2 ng/mL. Clinical stages of the enrolled patients were T1–T2N0M0 in 24, T3N0M0 in 6, N1M0 in one, and M1 in one, respectively. The median time to hot flush appearing after initiating hormone therapy was 5.5 months. In the beginning, patients received CMA at 100 mg orally per day. One doctor evaluated the curative effect four weeks later. We defined the evaluation of hot flush as disappeared (the symptom disappeared when conscious), improved (the symptom improve when conscious), not improved (the symptom did not improve when conscious). In patients with disappeared or improved symptoms, we decreased CMA dose to 50 mg per day. Four weeks later, we reevaluated the effect, and we decreased CMA dose to 25 mg per day. When hot flush appeared again at 25 mg per day, we returned the dose of CMA to 50 mg per day. Basically, CMA treatmet was continued as long as it was effective. In cases with no change for more than two months, we canceled the treatment of CMA. This study was approved by the Ethical Committee of Gunma University Hospital.

Patients	Disappeared	Improved	Not improved	Disappeared + Improved
32	17	10	5	84%

The average time to hot flush reduction : 1.16 months

[the progress of the patients with CMA]

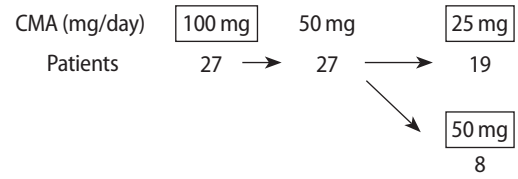

Fig. 1. The effect of chlormadine acetate (CMA).

Table 2. The average duration of the chlormadinone acetate (CMA) treatment in responsive case

CMA treatment	Duration (mo), average (range)
Monotherapy	26.8 (5–78)
Combination with radiation	16.4 (3–76)
Salvage	14.2 (4–24)

Table 3. The adverse events of chlormadinone acetate treatment

	No. (%)	Grade
Hyperhidrosis	1 (3.1)	2
ALT, AST increased	1 (3.1)	2

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

RESULTS

Hot flush disappeared in 17 patients, was improved in 10 patients, was not improved in 5 patients (reduction in 84% of hot flush patients). The median time to hot flush reduction was 1.16 months. The effect of CMA was maintained at 25 mg per day in 19 patients and at 50 mg per day in 8 patients (Fig. 1). The role of ADT in the patients enrolled in this study and average duration of CMA in patients with response of CMA were shown in Table 2. No patients had PSA failure in the treatment of CMA. Adverse events were mild as shown in Table 3.

DISCUSSION

A number of effective therapies are available for the management of hot flush [7]. Recently, Suzuki et al. [8] reported the clinical efficacy of milnacipran, serotonin-noradrenalin reuptake inhibitor (SNRI) in prostate cancer patients who suffer from hot flushes. It is reported that SNRI has a stronger effect for depression and less side effects in comparison with SSRI [9]. Their study included 12 patients who had taken hor-

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mone therapy for at least 3 months prior to the trial entry. At 12 weeks, 9 patients were available for the evaluation. Four patients received 50 mg per day and 5 patients received 25 mg per day. The patients with ≥50% decrease in baseline hot flash score were observed in 3 out of 4 who received 50 mg and 2 out of 5 who received 25 mg per day. The frequency of hot flushes had significantly decreased at the 12 weeks period than the baseline in the milnacipran 50 mg per day treatment group. These results indicated that milnacipran 50 mg per day therapy is effective in the treatment of hot flushes.

A previous study showed that the effect was comparatively high with corpus luteum hormone drug [10]. Irani et al. [11] reported a multicenter, randomized, double-blind study to compare the efficacy of venlafaxine, cyproterone acetate, and medroxyprogesterone acetate for the treatment of hot flushes in patients with prostate cancer who were being treated with GnRH analogues. They concluded after 6 months of treatment that leuprorelin, venlafaxine, cyproterone, and medroxyprogesterone were effective in reducing hot flushes. However, the hormonal treatments cyproterone and medroxyprogesterone were significantly more effective than venlafaxine. As cyproterone is a recognised treatment in prostate cancer, and its use could interfere with hormonal therapy, medroxyprogesterone could be considered to be the standard treatment for hot flushes in men undergoing androgen suppression for prostate cancer. In Japan, Sakai et al. [12] undertook a prospective, randomized study to longitudinally examine the status of the development of hot flushes in, and quality of life of, Japanese patients with prostate cancer who underwent combined androgen blockade (CAB) with a steroidal or nonsteroidal antiandrogen. They reported that the median frequencies of hot flushes daily were 1.3 and 2.2 for warmth/flushing (P=0.16) and 1.0 and 3.6 for sweating (P=0.021) in the chlormadinone and bicalutamide groups, respectively. Patients in the chlormadinone group were significantly less likely to be distressed by warmth/flushing (odds ratio, 0.47; P<0.001) and sweating (odds ratio, 0.61; P=0.01) than those in the bicalutamide group. They concluded that CAB using a steroidal antiandrogen such as chlormadinone might induce fewer and less-distressing hot flushes than CAB with bicalutamide. These finding prompted us to use CMA for prostate cancer patients who had severe hot flush in during treatment with GnRH analogues. In this study, reduction in 84% of hot flush patients was observed. There are not many reports in which CMA was used for hot flush during treatment with GnRH analogue. Suzuki et al. [13,14] evaluated the incidence of hot flushes in sixty-eight prostate cancer patients receiving endocrine therapy. The overall incidence of hot flushes was 37%, and hot flushes improved after 4 weeks in 3 of 4 patients (75%) treated by CMA. They used CMA again for ten hot flush patients later. Hot flushes improved after 4 weeks in 9 of 10 patients (90%).

With regard to problems concerning the CMA dosage, using steroidal anti androgen in MAB treatment has been identified as disadvantageous by meta-analysis [15,16]. The results for cyproterone acetate, which accounted for only a fifth of the evidence, appeared slightly unfavorable to MAB (5-year survival, 15.4% with MAB vs. 18.1% with androgen suppression [AS] alone; difference, –2.8% [standard error {SE}, 2.4]; log-rank, P=0.04 adverse), whereas those for nilutamide and flutamide appeared slightly favorable (5-year survival, 27.6% with MAB vs. 24.7% with AS alone; difference, 2.9% [SE, 1.3]; log-rank, P=0.005) [15]. Sakai et al. [12] stated that, from the viewpoint of safety, chlormadinone, not cyproterone, was developed as a therapeutic drug for prostate cancer in Japan, but because their study had a limited duration of 2 years, the difference in survival time between the treatment groups was not assessed. Against such a background, we carried out gradual decrease of dose of CMA to avoid disadvantageous effects for prostate cancer treatment. Although the usual dose of CMA for prostate cancer is 100 mg/day, hot flush disappeared in all patients at 50 mg/day. Furthermore, the effect of CMA was maintained at 25 mg/day in many patients. In addition, no patients had PSA failure in the treatment of CMA. Considering the above, the gradual decrease of dose of CMA may be appropriate for treating hot flush.

The limitation of this study is the relative small number of enrolled patients, and the one-armed observation study. We are planning to add the number of patients, and to reevaluate the efficacy of CMA.

In conclusion, when hot flush appears during treatment with LH-RH agonist for prostate cancer, CMA might improve hot flush. If the effect of CMA is maintained, low dose CMA might be used.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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