Hot flashes during androgen deprivation therapy with a luteinizing hormone-releasing hormone agonist combined with steroidal or nonsteroidal antiandrogens for prostate cancer

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ABSTRACT

Objectives: We conducted a prospective, randomized study to investigate hot flashes and quality of life (QOL) during combined androgen blockade (CAB) therapy using steroidal or nonsteroidal antiandrogens.

Methods: A total of 151 patients with prostate cancer, enrolled into this study between May 2001 and June 2003, were randomized to receive CAB therapy using an LHRH agonist (leuprorelin) combined with a steroidal antiandrogen (chlormadinone) or a nonsteroidal antiandrogen (bicalutamide). The incidence of, frequency of, and distress due to hot flashes were evaluated with a self-entry questionnaire over 2 years. General and disease-specific QOL outcomes were also measured with the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire.

Results: Data were available for analysis on 124 patients. Although the incidence of hot flashes largely tended to be higher in the bicalutamide group than in the chlormadinone group, no significant difference was noted in the cumulative incidence of hot flashes at 2 years. The median frequency of hot flashes per day was 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 due to warmth/flushing

(OR 0.47, $P < 0.001$) and sweating (OR 0.61, $P = 0.01$) than those in the bicalutamide group. The time course of FACT-P scores showed no inter-group differences.

Conclusions: Our results suggest that CAB using a steroidal antiandrogen such as chlormadinone may induce fewer and less distressing hot flashes than CAB with bicalutamide.

INTRODUCTION

A hot flash is a sudden, temporary onset of body warmth and may be accompanied by flushing and sweating. Hot flashes are the most common symptom in menopausal women and are also a common and potentially chronic problem in men with prostate cancer who undergo androgen deprivation therapy (ADT).[1] Up to 80% of patients treated with a luteinizing hormone-releasing hormone (LHRH) agonist report hot flashes, and up to 27% report this as the most troublesome adverse effect.[2] Hot flashes can significantly affect quality of life (QOL) for men undergoing ADT. However, the characteristics of hot flashes in men undergoing ADT have not been widely studied.[1]

Methods to avoid or reduce these unpleasant side effects as much as possible have been investigated. In particular, the hot flash-preventive and -improving effects of steroidal antiandrogens have been reported.[3,4] Chlormadinone acetate (chlormadinone), which we used in the present study, is a steroidal antiandrogen that is used in combined androgen blockade (CAB) therapy as well as monotherapy for prostate cancer in Japan. A double-blind controlled study[5] has verified the therapeutic equivalence of bicalutamide and chlormadinone.

Based on the above background, we conducted the present prospective, randomized study to longitudinally examine the status of the development of hot flashes in and QOL of Japanese

patients with prostate cancer who underwent CAB with a steroidal or nonsteroidal antiandrogen.

MATERIAL AND METHODS

ELIGIBILITY

All eligible patients had histologically confirmed adenocarcinoma of the prostate, with localized or metastatic disease; a Southwest Oncology Group performance status score from 0 to 3 on a scale of 0 to 4; a life expectancy of at least three months; and adequate organ function. Disease stage and histological grade were assessed by the 1997 TNM staging system. Patients with an active synchronous cancer were excluded. Eligible patients had had no previous treatment for prostate cancer.

STUDY DESIGN

This study was designed as a prospective, randomized, open-label trial of CAB with a steroidal antiandrogen versus CAB with a nonsteroidal antiandrogen. Patients were randomly assigned to receive either a combination of an LHRH agonist (leuprorelin) and a steroidal antiandrogen (chlormadinone) or a combination of leuprorelin and a nonsteroidal antiandrogen (bicalutamide) by the minimization method of balancing the groups according to clinical stage, grade of

histological differentiation, and performance status. A 3.75 mg depot of leuprorelin was administered subcutaneously once every four weeks, and 100 mg of chlormadinone or 80 mg of bicalutamide were given orally, starting two weeks before the first dose of leuprorelin. The primary endpoints were the incidence, frequency, and severity of hot flashes and the QOL during CAB therapy using steroidal or nonsteroidal antiandrogens.

The study protocol was approved by the Clinical Trial Review Committee of the Nagasaki Prostate Cancer Research Group (NPCRG) and the institutional review board of each participating institution before the initiation of the study, and all of the patients provided written informed consent before randomization.

ASSESSMENTS

An originally prepared questionnaire was used to survey the patients regarding the frequency of hot flashes, timing of their development, and level of discontent about hot flashes. The patient was asked to select one of the following options for the question, "How would you feel if warmth/flushing or sweating persists for life?": "Very discontent (1)", "Discontent (2)", "Slightly discontent (3)" or "Unanxious (4)". The Japanese version[6] of the Functional Assessment of Cancer Therapy-Prostate (FACT-P),[7] the validity of which has been verified, was used to evaluate QOL of the patients. Hot flashes and QOL were evaluated according to the

self-administered system. Timing for survey was as follows: at baseline; at the first administration of leuprorelin; every 2 weeks thereafter up to week 12; and every 3 months thereafter. The observation period had to last for 2 years.

All eligible patients underwent a baseline history taking and physical examination, a complete blood count, blood-chemistry studies, urinalysis, and measurement of PSA. These studies were conducted at baseline, at weeks 4, 8, and 12, and every 3 months thereafter. Patients underwent chest radiography, transrectal ultrasonography of the prostate, radionuclide bone scanning, and CT of the abdomen and pelvis at baseline and at 3, 12, and 24 months later.

Differences in the distributions of the background variables, and incidence, timing, frequency and severity of hot flashes were evaluated using $\chi 2$ or Mann–Whitney *U* tests. QOL scores for the various domains are shown as the mean ± SD, with a higher score always representing a better QOL. Repeated measure analyses of variance (ANOVA) were used to compare QOL scores between treatment groups. All *P* values reported are two-tailed, and $P < 0.05$ was considered significant.

RESULTS

In the present study 151 patients with prostate cancer were registered, 76 and 75 of whom were

assigned to the chlormadinone and bicalutamide groups, respectively. Among them, there were 11 patients who were found to be ineligible after enrollment and 2 patients who refused treatment after assignment. Moreover, no data were reported after randomization in 14 patients. After removing these patients, a total of 124 patients, that is, 60 in the chlormadinone group and 64 in the bicalutamide group, were subject to analyses. No statistically significant difference was found in the background variables between the two groups (Table 1).

A significant difference was found in the timing of hot flashes between the two groups ($P < 0.001$, Table 2). Patients in the chlormadinone group experienced both warmth/flushing and sweating more often during sleep, whereas patients in the bicalutamide group experienced these symptoms more often when feeling tension. The median frequency of sweating was significantly lower in the chlormadinone group than in the bicalutamide group (1.0 vs. 3.6 episodes/day, respectively, $P = 0.021$), although there was no significant difference in the frequency of warmth/flushing between the two groups (1.3 vs. 2.2 episodes/day, respectively, $P = 0.16$, Table 2). A significant difference was found between the two groups with respect to the level of discontent about warmth/flushing ($P < 0.001$) and sweating ($P = 0.027$, Table 2). The percentage of patients who felt some discontent throughout the treatment period (all patients except those who gave a reply of “unanxious” and hot flash-free patients) based on the cumulated number of replies yielded the following values: for warmth/flushing, 8.2% in the chlormadinone group and

16.1% in the bicalutamide group; for sweating, 8.2% in the chlormadinone group and 12.7% in the bicalutamide group. Therefore, the discontent levels were significantly lower in the chlormadinone group (for warmth/flushing, odds ratio: 0.47 and $P < 0.001$; and for sweating, odds ratio: 0.61 and $P = 0.01$).

The incidences of warmth/flushing were lower in the chlormadinone group than in the bicalutamide group throughout the treatment period; significant differences were found at week 8 ($P = 0.049$), week 10 ($P = 0.029$), month 6 ($P = 0.007$) and month 9 ($P = 0.023$). The incidence of sweating was lower in the bicalutamide group at the early stage of treatment and in the chlormadinone group at week 10 or thereafter, but the difference was not statistically significant (Fig. 1). Also, there was no significant difference in the cumulative incidence of hot flashes at 2 years for warmth/flushing, 43.3% and 51.4% ($P = 0.51$) or for sweating, 51.7% and 48.5% ($P = 0.80$) in the chlormadinone and bicalutamide groups, respectively. The time-course changes in FACT-P total showed no changes of clinical relevance, and no significant difference was observed between the two groups. There were also no clinically significant time-course changes in any of the domains (Table 3).

Relapse occurred in six patients in the chlormadinone group and 10 in the bicalutamide group during the treatment period. Furthermore, there were four deaths (two from cancer and two from other causes of death) in the chlormadinone group and two deaths (one from cancer and one from

another cause of death) in the bicalutamide group.

The major toxic effects rated grade 2 or higher except for hot flashes were hepatic dysfunction in eight patients (13.3%) in the chlormadinone group, and anemia in two (3.1%) and diarrhea in two (3.1%) in the bicalutamide group. Consequently administration of chlormadinone was discontinued due to hepatic dysfunction in five patients. After administration was discontinued, the hepatic function was normalized in all patients. On the other hand, administration of bicalutamide was discontinued due to diarrhea in two patients, which was followed by full recovery.

COMMENT

Many studies have reported decreased QOL in hormonal therapy,[8-11] which is mostly considered attributable to androgen deprivation-induced side effects, e.g., hot flashes, sexual dysfunction, weight gain, muscle weakness, anemia, osteoporosis, depression and gynecomastia. Recently, hot flashes have elicited concern as a factor that lowers QOL. Charig *et al.*[9] reported that castration provoked hot flashes in 76% of patients, that one-third of them had severe hot flashes, and that the mean duration of disease was as long as 33 months. Furthermore, Carpenter *et al.*[10] used the SF-12 to evaluate QOL and reported that hot flashes tended to cause QOL to deteriorate in

relation to mental health and physical function. However, all of these studies were conducted using a cross-sectional design. Therefore, Basaria *et al.*[8] indicated the need to conduct a longitudinal study in order to clarify the relationship between the timing/severity of adverse events and QOL.

In our prospective, randomized controlled study, the level of discontent about hot flashes was approximately twofold greater in the bicalutamide group than in the chlormadinone group. The difference in the number of episodes of hot flashes per day seemed to have affected the difference in level of discontent between the two groups. Therefore, hot flashes were shown to be a factor that lowers QOL. In consideration of the above arguments, the magnitude of a QOL decrease due to hot flashes was considered to be greater in the bicalutamide group than in the chlormadinone group. However, despite a significant difference between the two groups with respect to the severity of hot flashes, the time course of the FACT-P total and each of the domain scores showed no inter-group differences. Although hot flashes appear to reduce QOL, it is likely to be difficult to evaluate the degree of adverse effects due to hot flashes on QOL using the FACT-P questionnaire.

Although the pathophysiology of hot flashes remains unknown, a decline in sex hormone concentrations might lead to alterations in brain neurotransmitters and to instability in the hypothalamic thermoregulatory setpoint[1]. In the present study, although all patients were

medically castrated, there were considerable differences in the clinical feature of hot flashes between the two treatment groups. Bicalutamide is a pure antiandrogen, whereas chlormadinone is a progestin with progestational as well as antiandrogenic properties, which might partly explain the clinical differences between the two antiandrogens. In fact, various studies have demonstrated that progestins can ameliorate hot flashes in menopausal women[12-14] and in men who have undergone ADT for prostate cancer.[4] Although the mechanism of action of progestins in controlling hot flashes is unknown, it has been reported that progesterone inhibits most warm-sensitive neurons directly or indirectly via local neuronal circuits in the preoptic area of the hypothalamus in male and female rats.[15]

Although no significant difference was found between the two groups with respect to 2-year progression-free survival (data not shown), the effects of the combination with chlormadinone on survival rate should be evaluated in a study of longer duration that takes the following into account: 1) as described in one report[16] the survival rate differs between CAB with a steroidal antiandrogen and CAB with a nonsteroidal antiandrogen; and 2) from the viewpoint of safety, chlormadinone, not cyproterone, was developed as a therapeutic drug for prostate cancer in Japan.

Hot flashes impair the QOL of patients treated with ADT, and our results suggest that CAB using a steroidal antiandrogen may induce fewer and less distressing hot flashes than CAB with a

nonsteroidal antiandrogen. Since the present study has a limited duration of 2 years, the difference in survival time between the treatment groups was not assessed. A combined assessment of quality and quantity of life over a longer period of time is needed in ADT for patients with prostate cancer.

REFERENCES

1. Stearns V, Ullmer L, Lopez JF, et al: Hot flushes. Lancet 2002; 360: 1851-1861.
2. Holzbeierlein JM, McLaughlin MD, Thrasher JB: Complications of androgen deprivation therapy for prostate cancer. Curr Opin Urol 2004; 14: 177-183.
3. Thorpe SC, Azmatullah S, Fellows GJ, et al: A prospective, randomized study to compare goserelin acetate (Zoladex) versus cyproterone acetate (Cyprostat) versus a combination of the two in the treatment of metastatic prostatic carcinoma. Eur Urol 1996; 29: 47-54.
4. Loprinzi CL, Michalak JC, Quella SK, et al: Megestrol acetate for the prevention of hot flashes. N Engl J Med. 1994; 331: 347-352.
5. Kotake T, Usami M, Akaza H, et al: Clinical evaluation of bicalutamide (Casodex) in patients with prostate cancer. A double-blind trial of bicalutamide versus chlormadinone acetate. Jpn J Urol Surg 1996; 9: 243-256.

6. Hinotsu A, Niimi M, Akaza H, et al: Development of Japanese version of QOL questionnaire for bladder and prostate cancer patients using FACT-Bl and P: pilot study. Gan To Kagaku Ryoho 1999; 26: 657-666.

7. Esper P, Mo F, Chodak G, et al: Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology 1997; 50: 920–928.

8. Basaria S, Lieb J 2nd, Tang AM, et al: Long-term effects of androgen deprivation therapy in prostate cancer patients. Clin Endocrinol 2002; 56: 779-786.

9. Charig CR, Rundle JS: Flashing. Long-term side effect of orchiectomy in treatment of prostatic carcinoma. Urology 1989; 33: 175-178.

10. Carpenter JS, Andrykowski MA, Cordova M, et al: Hot flashes in postmenopausal women treated for breast carcinoma: prevalence, severity, correlates, management, and relation to quality of life. Cancer 1998; 82: 1682-1691.

11. Jonler M, Nielsen OS, Groenvold M, et al: Quality of life in patients with skeletal metastases of prostate cancer and status prior to start of endocrine therapy: results from the Scandinavian Prostate Cancer Group Study 5. Scand J Urol Nephrol 2005; 39: 42-48.

12. Morrison J, Martin D, Blair R, et al: The use of medroxyprogesterone acetate for relief of climacteric symptoms. Am J Obstet Gynecol 1980; 138: 99-104.

13. Schiff I, Tulchinsky D, Cramer D, et al: Oral medroxyprogesterone in the treatment of menopausal symptoms. JAMA 1980; 244: 1443-1445.

14. Goodwin JW, Green SJ, Moinpour CM, et al: Phase III randomized placebo-controlled trial of two doses of megestrol acetate as treatment for menopausal symptoms in women with breast cancer: Southwest Oncology Group Study 9626. J Clin Oncol 2008; 26: 1650-1656.

15. Tsai CL, Matsumura K, Nakayama T: Effects of progesterone on thermosensitive neurons in preoptic slice preparations. Neurosci Lett 1988; 86: 56-60.

16. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet 2000; 355: 1491-1498.

Table 1. Baseline characteristics of eligible patients

Characteristic	Chlormadinone (n = 60)	Bicalutamide (n = 64)	P value
Age (yr)			
Median	74.2	75.7	0.88
Mean ± SD	74.6 ± 6.9	74.8 ± 5.7	
Performance status (n, %)			0.60
0 - 1	59 (98.3)	62 (96.9)	
2 - 3	1 (1.7)	2 (3.1)	
TNM classification (n, %)			0.23
T1-2N0M0	27 (45.0)	24 (37.5)	
T3-4N0M0	19 (31.7)	24 (37.5)	
N1M0	6 (10.0)	2 (3.1)	
M1	8 (13.3)	14 (21.9)	
Histological grade (n, %)			0.30
G1	15 (25.0)	10 (15.6)	
G2	28 (46.7)	38 (59.4)	
G3-4	17 (28.3)	16 (25.0)	
Serum PSA (ng/ml)			0.62
Median	22.8	29.8	
Mean ± SD	103.7 ± 171.1	135.4 ± 476.0	
Comorbid disease (n, %)			0.31
Absent	39 (65.0)	47 (73.4)	
Present	21 (35.0)	17 (26.6)	

Table 2. Frequency, timing, and severity of hot flashes

	Chlormadinone	Bicalutamide	*P* value
Frequency (episodes/day)			
Warmth/flushing (median, IQR)	1.3 (1.0-3.4)	2.2 (1.1-5.0)	0.16
Sweating (median, IQR)	1.0 (0.8-3.3)	3.6 (2.2-5.2)	0.021
Timing			
Warmth/flushing (*n**, %)			<0.001
During sleep	18 (24.7)	15 (7.4)	
At bed time	4 (5.5)	10 (4.9)	
On feeling tension	3 (4.1)	38 (18.7)	
Not in a specific time	43 (58.9)	121 (59.6)	
Others	5 (6.8)	19 (9.4)	
Sweating (*n**, %)			<0.001
During sleep	46 (52.3)	18 (12.2)	
At bed time	2 (2.3)	6 (4.1)	
On feeling tension	8 (9.1)	28 (18.9)	
Not in a specific time	26 (29.5)	85 (57.4)	
Others	6 (6.8)	11 (7.4)	
Severity			
Warmth/flushing (*n**, %)			<0.001
Very discontent	16 (2.7)	29 (4.0)	
Discontent	19 (3.3)	41 (5.6)	
Slightly discontent	13 (2.2)	48 (6.5)	
Unanxious	14 (2.4)	43 (5.9)	
Absent	521 (89.4)	573 (78.1)	
Sweating (*n**, %)			0.027
Very discontent	19 (3.4)	20 (3.0)	
Discontent	14 (2.5)	29 (4.4)	
Slightly discontent	13 (2.3)	35 (5.3)	
Unanxious	29 (5.1)	35 (5.3)	
Absent	490 (86.7)	544 (82.1)	

*Cumulated number of replies.

Table 3. FACT-P total and subscale scores according to the treatment group

	Chlormadinone	Bicalutamide	*P* value
FACT-P total			0.83
Baseline	113.7 ± 23.6	111.7 ± 27.2	
3 mo	116.2 ± 24.4	118.2 ± 24.1	
6 mo	116.4 ± 23.0	116.9 ± 29.6	
9 mo	114.1 ± 23.4	120.1 ± 23.1	
12 mo	114.6 ± 22.4	116.4 ± 24.3	
18 mo	116.4 ± 21.0	116.5 ± 22.8	
24 mo	116.2 ± 20.3	118.3 ± 24.1	
Physical well-being			0.64
Baseline	24.7 ± 4.1	23.6 ± 5.9	
3 mo	23.7 ± 4.8	24.2 ± 4.0	
6 mo	23.6 ± 5.0*	24.3 ± 4.7	
9 mo	22.8 ± 6.5*	24.6 ± 4.0	
12 mo	23.0 ± 5.5*	24.0 ± 4.4	
18 mo	23.7 ± 5.8	24.2 ± 4.3	
24 mo	23.8 ± 4.8	23.1 ± 5.7	
Social/family well-being			0.50
Baseline	23.3 ± 9.8	22.3 ± 10.6	
3 mo	23.0 ± 8.7	21.2 ± 9.5	
6 mo	23.3 ± 8.1	21.4 ± 9.3	
9 mo	23.3 ± 8.1	21.2 ± 9.7	
12 mo	22.7 ± 8.8	21.3 ± 8.7	
18 mo	21.1 ± 9.9	21.1 ± 8.4*	
24 mo	21.0 ± 9.3	21.9 ± 9.0	
Emotional well-being			0.63
Baseline	18.1 ± 3.8	17.2 ± 5.0	
3 mo	18.5 ± 4.4	19.2 ± 4.0†	
6 mo	19.0 ± 4.2	19.6 ± 4.2†	
9 mo	17.8 ± 4.8	19.7 ± 3.8†	
12 mo	18.4 ± 4.3	19.1 ± 4.3*	
18 mo	19.4 ± 4.5*	19.6 ± 4.1*	
24 mo	18.7 ± 4.9	18.9 ± 4.3	
Functional well-being			0.41
Baseline	18.2 ± 8.0	18.6 ± 8.8	
3 mo	20.0 ± 7.1	19.9 ± 7.4	
6 mo	19.4 ± 7.3	20.4 ± 7.3	
9 mo	18.7 ± 8.3	20.7 ± 7.5	
12 mo	17.9 ± 8.2	20.0 ± 7.5	
18 mo	18.3 ± 8.2	20.2 ± 7.1	
24 mo	19.8 ± 6.6	21.7 ± 6.3	
Additional concerns			0.83
Baseline	31.6 ± 7.8	30.6 ± 9.2	
3 mo	33.5 ± 6.2	34.3 ± 7.0†	
6 mo	34.3 ± 6.0*	34.7 ± 8.3†	
9 mo	32.4 ± 7.2	34.2 ± 7.7*	
12 mo	32.6 ± 7.1	33.0 ± 9.2	
18 mo	33.9 ± 6.3	32.2 ± 7.5	
24 mo	32.8 ± 6.5	32.7 ± 8.4	

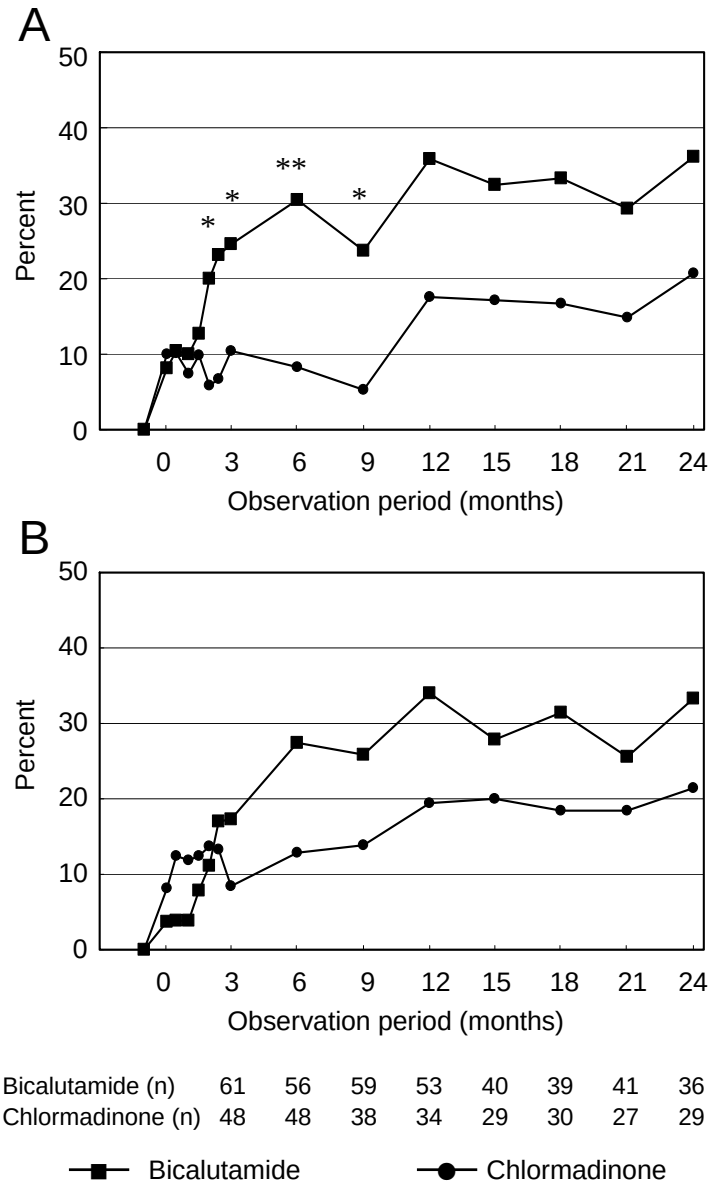
Data presented as mean ± standard deviation.

* $P < 0.05$, statistically significant change from baseline.

† $P < 0.01$, statistically significant change from baseline.

Legend to Figure 1

Longitudinal changes in the incidence of warmth/flushing (A) and sweating (B). The incidences of warmth/flushing were significantly lower in the chlormadinone group than in the bicalutamide group at week 8 ($P = 0.049$), week 10 ($P = 0.029$), month 6 ($P = 0.007$) and month 9 ($P = 0.023$).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