Original Article

Efficacy of keishibukuryogan for hot flashes in prostate cancer patients receiving androgen deprivation therapy: a sub-analysis focusing on hormonal and cytokine levels

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Background: The current study attempted to elucidate the mechanisms of keishibukuryogan (TJ-25) efficacy by focusing on hormonal and cytokine levels. This is a sub-analysis of serum hormonal and cytokine levels extracted from the single-arm prospective study.

Methods: Twenty-five participants were administrated TJ-25 at a dose of 2.5 g three times daily for 12 weeks, and competed for a diary of their hot flashes conditions. Various hormonal and cytokine values, including interleukin (IL)-8 and tumor necrosis factor-α (TNF-α), were measured at the baseline and 12-week visits. The correlation of hot flashes with hormonal and cytokine levels at baseline was investigated. As part of the responder analyses, all participants were divided into two groups based on the median baseline values of all hormones and cytokines at baseline, and the change amounts in strength and frequency of hot flashes from baseline to 12-week visits in both groups were compared. Furthermore, a correlation in change amounts (Δ values) by TJ-25 administration between hot flashes and each parameter was also conducted.

Results: Hot flashes intensity was inversely related to estradiol levels (r=–0.433, P=0.019), and frequency was inversely related to progesterone levels (r=–0.415, P=0.025). In the responder analyses, the effectiveness of TJ-25 for hot flash strength increased in the patients with higher levels of TNF-α at baseline (P=0.0372). TJ-25 was more efficient in frequency in the patients with higher levels of IL-8 (P=0.0312). TJ-25 efficacy, on the other hand, was not significantly associated with changes in any hormonal or cytokine levels between the baseline and 12-week visits. However, ΔIL-8 and ΔTNF-α were not significantly correlated with Δstrength and Δfrequency of hot flashes by TJ-25 administration.

Conclusions: Hot flashes were inversely correlated with estradiol and progesterone levels. TJ-25 was more effective in patients with higher TNF-α and IL-8 levels, with no significant change in serum levels caused by the treatment. The suggestive mechanism for the effects of keishibukuryogan is that this drug doesn't suppress the production of IL-8 and TNF-α, but may inhibit some actions of these cytokines.

Keywords: Prostate cancer; hot flashes; keishibukuryogan; cytokines; sex hormones

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Introduction

Treatment options for prostate cancer (PC), one of the most common cancers in man globally, are generally divided into hormonal therapy, prostatectomy, and radiotherapy, and these options are often chosen for each patient in consideration of the quality of life (QOL) and some complications associated with treatments, such as erectile dysfunction and urinary incontinence (1). Androgen deprivation therapy (ADT), which is medical castration by luteinizing hormone-releasing hormone (LH-RH) agonists or LH-RH antagonists combined with androgen blockade (CAB) therapy, is the most commonly used hormonal therapy for PC. In Japan, ADT is most commonly used, particularly in the elderly or patients with multiple complications (2,3).

In recent years, not only the efficiency of hormone therapy but also its adverse effects have attracted attention. Hot flashes were observed in approximately 80% of hormone therapy patients, which can frequently result in a decrease in QOL (4). Although the effectiveness of some agents for hot flashes caused by ADT has been reported (5,6), none have been presently established.

Keishibukuryogan, a Japanese traditional herbal medicine, is used to treat menopausal symptoms (headache, dizziness, hot flashes, stiff shoulders, etc.), and, has been used to treat hot flashes in hypogonadal men (7,8). Keishibukuryogan (TJ-25, TSUMURA & CO, Tokyo, Japan) was found to be an efficient and safe treatment for hot flashes in PC patients receiving ADT in a previous prospective study (9). However, the mechanisms of the efficacy of TJ-25 for hot flashes have been not well understood. We attempted to elucidate the mechanisms of TJ-25 efficacy by focusing on hormonal and cytokine levels in the current study. We present this article following the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-121/rc).

Highlight box

Key findings

- Keishibukuryogan was more effective in patients with higher levels of TNF-α (P=0.0372) and IL-8 (P=0.0312) during androgen deprivation therapy for prostate cancer, with no significant change quantities of these blood levels by the medication.

What is known and what is new?

- Keishibukuryogan is an efficient and safe treatment for hot flashes in patients receiving androgen deprivation therapy.
- The present study elucidated hormonal and cytokine conditions in the patients with hot flashes, and showed that some effects of keishibukuryogan was potentially correlated with serum IL-8 and TNF-α.

What is the implication, and what should change now?

- Keishibukuryogan may prevent some of the actions of IL-8 and TNF-α, rather than suppressing their production, which is one possible mechanism for its effects.

Methods

Study subjects

The current study is a sub-analysis of serum hormonal and cytokine levels extracted from the single-arm prospective study (UMIN 000031606) that evaluated the efficacy and safety of TJ-25 for hot flashes in PC patients receiving ADT (9). According to the study protocol, all participants were given TJ-25 at a dose of 2.5 g three times per day for 12 weeks (9). During the trial, all patients competed for a diary of their hot flashes conditions. The diary contained information on the strength and frequency. The intensity of hot flashes was measured using a visual analog scale (VAS) and quantified using a 100 mm VAS ruler Frequency was counted by the number of hot flashes per day. The strength and frequency of hot flashes were evaluated as the mean value recorded in a diary for 1 week before baseline and a 12-week visit.

Participants provided clinical information at the outset, including body mass index, duration of PC, clinical stage of PC, use of LH-RH agonist or antagonist, and presence of radical prostatectomy, radiation, and complications. At baseline and 12-week visits, various hormonal [total testosterone (TT), dehydroepiandrosterone (DHEA), dihydrotestosterone (DHT), all patients had [interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), macrophage chemotactic protein-1 (MCP-1, also known as CCL2), macrophage inflammatory protein-1β (MIP-1β, also known as CCL-4), and vascular endothelial growth factor (VEGF)] levels measured.

All participants provided written informed consent following a protocol approved by the Ethics Committee of the Kanazawa University Graduate School of Medical Science (No. 2017-214), and the study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Table 1 Baseline patients' background (n=25)

Variables	Mean ± SD or number
Age (years)	69.5±6.0
BMI (kg/m^2)	24.0±3.7
PSA levels (ng/mL)	0.1±0.3
Gleason score	9.2±0.9
TNM stage	
T1	1
T2	9
T3	12
T4	3
N	
N0	20
N1	5
M	
M0	21
M1	4
Duration of prostate cancer (years)	2.8±3.2
Hormonal therapy	
LH-RH agonist	19
LH-RH antagonist	6
Anti-androgenic therapy*	20
Radical radiation therapy	9
Prostatectomy	7
Complications	6
Strength of hot flashes (VAS) (mm)	51.8±21.3
Frequency of hot flashes (times/day)	4.2±2.2

*, all cases used bicaltamide. BMI, body mass index; PSA, prostate specific antigen; LH-RH, luteinizing hormone-releasing hormone; VAS, visual analogue scale.

Laboratory assays

All blood samples were collected between 09:00 and 11:00 in the morning at each visit. Blood samples were immediately centrifuged at 4 ℃, and serum was kept at −80 ℃ until assays were performed. Each laboratory received aliquots of each serum sample. Each hormone value was measured by Liquid Chromatograph - Mass Spectrometry (LC-MS/MS) (ASKA Pharma Medical Co., Ltd., Kanagawa, Japan). Each cytokine level was assessed in a TSUMURA & CO laboratory using a Bio-Plex Suspension Array System (Bio-Rad Laboratories, Hercules, CA, USA) and Luminex xMAP technology.

Sample size

This was a sub-analysis of a prospective observational pilot study (9). In the original study, the sample size had been calculated based on the number of patients undergoing hormone therapy per year at research facilities and incidence rate of hot flashes.

Statistical analysis

Initially, changes in hormone and cytokine levels from baseline to 12-week visit were analyzed by paired *t*-test. A correlation between the strength and consistency of hot flashes was examined by Spearman's test. To elucidate the link between hormones or cytokines and hot flashes, the correlation of hot flashes with hormonal and cytokine levels at baseline was also examined employing Spearman's test.

Next, we tried to examine the predictive factors for response to TJ-25 for hot flashes. According to the baseline median values of every hormone and cytokine, all subjects were split into two groups. The changes from baseline to 12-week visit in strength and frequency of hot flashes in both groups were compared by unpaired *t*-test. Furthermore, the relationship in change amounts (Δ values) by TJ-25 administration between hot flashes and each parameter was also conducted using Spearman's test.

Two-tailed analysis was carried out in all analyses, and then a P value of <0.05 shows statistical significance.

Results

Patients characteristics

Twenty-five patients who completed 12-week treatment were included in the present sub-analysis. The age [mean ± standard deviation (SD)] of a total of 25 participants was 69.5±6.0 years (*Table 1*). As shown in our previous study (9), mean values of VAS and frequency of hot flashes were 51.8±21.3 and 4.2±2.2 at baseline, and 37.6±15.8 and 3.7±2.0 at the 12-week visit, and TJ-25 treatment for 12 weeks had significantly improved strength and frequency of hot flashes. Hormone and cytokine levels at baseline and 12-week visit are shown in *Table 2*. No significant changes in all

Table 2 Hormone and cytokine levels at baseline and 12-week visit

Variables	Baseline, mean ± SD (median)	12-week visit, mean ± SD	P value
Hormone			
Testosterone (ng/dL)	74.2±40.9 (61.6)	79.1±63.3	0.737
DHT (ng/dL)	10.5±9.0 (7.1)	11.6±8.7	0.514
Estradiol (pg/mL)	1.7±0.8 (1.7)	1.5±0.5	0.318
DHEA (ng/mL)	1.2±0.7 (1.1)	1.2±0.7	1.000
Progesterone (ng/mL)	14.3±7.7 (13.2)	16.2±8.0	0.261
Cytokine			
IFN-γ (IU/mL)	29.7±33.9 (16.1)	31.4±30.9	0.766
IL-1β (pg/mL)	10.2±21.3 (3.0)	11.3±24.8	0.513
IL-2 (pg/mL)	4.8±7.0 (2.4)	5.4±8.0	0.378
IL-4 (pg/mL)	62.2±83.1 (30.5)	70.0±87.8	0.599
IL-6 (pg/mL)	3.4±3.5 (1.6)	3.7±4.0	0.563
IL-8 (pg/mL)	4.1±2.5 (2.8)	4.1±2.6	0.939
IL-10 (pg/mL)	29.0±51.7 (10.6)	30.3±39.8	0.809
MCP-1 (pg/mL)	229.4±71.9 (209.1)	242.9±66.1	0.256
MIP-1β (pg/mL)	43.3±30.1 (30.0)	46.8±36.5	0.490
TNF-α (pg/mL)	19.4±14.3 (13.3)	20.5±12.2	0.702
VEGF (pg/mL)	161.4±103.9 (129.8)	176.4±100.3	0.446

SD, standard deviation; DHT, dihydrotestosterone; DHEA, dehydroepiandrosterone; IFN, interferon; IL, interleukin; MCP, macrophage chemotactic protein; MIP, macrophage inflammatory, protein; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

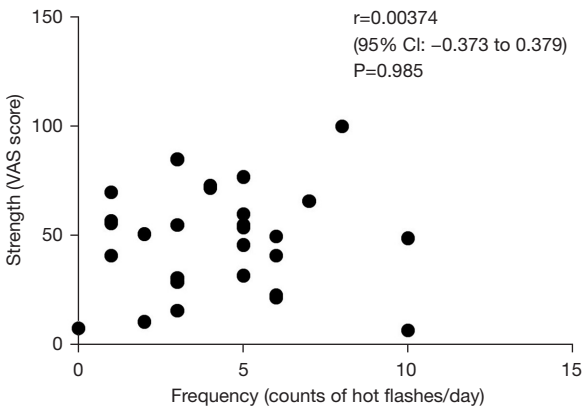

Figure 1 A relationship between VAS and the frequency of hot flashes before the treatment was indicated. No significant correlation between VAS and the frequency of hot flashes was not found. VAS, visual analog scale.

of hormone and cytokine levels were observed by TJ-25 treatment.

Initially, we investigated whether or not the intensity and frequency of hot flashes should be considered separately. Prior to treatment, there was no discernible relationship between VAS and hot flash frequency (r=0.00374, 95% CI: −0.373 to 0.379, P=0.985) (*Figure 1*). As a result, hot flashes were examined separately for strength and frequency in the present study.

The relationship between the intensity and frequency of hot flashes and hormone/cytokine levels

Strength was inversely correlated with estradiol levels (r=−0.433, P=0.019), and frequency revealed an inverse correlation with progesterone levels (r=−0.415, P=0.025)

Table 3 The relationship between the intensity and frequency of hot flashes and each hormone level

	Testosterone	DHEA	DHT	Estradiol	Progesterone
Strength (VAS)					
r	–0.139	0.051	0.187	–0.433	–0.041
P value	0.471	0.795	0.332	0.019*	0.833
Frequency					
r	–0.315	–0.105	0.041	–0.044	–0.415
P value	0.096	0.588	0.835	0.821	0.025*

*, significant difference (two-tailed test). VAS, visual analog scale; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone.

Table 4 The correlation between each cytokine level and the strength/frequency of hot flashes

	IL-1β	IL-2	IL-4	IL-6	IL-8	IL-10	TNF-α	IFN-γ	MCP-1	MIP-1β	VEGF
Strength (VAS)											
r	0.259	0.065	0.206	0.238	0.066	0.119	0.146	0.109	0.161	0.088	–0.006
P value	0.175	0.736	0.284	0.214	0.734	0.538	0.45	0.572	0.405	0.649	0.974
Frequency											
r	–0.075	0.11	0.061	0.182	0.33	0.071	0.194	0.153	0.237	0.239	–0.012
P value	0.7	0.57	0.755	0.346	0.08	0.715	0.313	0.429	0.216	0.212	0.951

VAS, visual analog scale; IL, interleukin; TNF, tumor necrosis factor; MCP, macrophage chemotactic protein; MIP, macrophage inflammatory protein; VEGF, vascular endothelial growth factor.

(*Table 3*). However, there were no significant correlations between hot flashes symptoms and all of the cytokine levels (*Table 4*).

Responder analysis based on hormone/cytokine levels

All subjects were divided into two groups according to the baseline median values (*Table 2*) of every hormone and cytokine, and the responder analysis was performed. The efficacy of TJ-25 for the strength of hot flashes was significantly correlated with higher levels of TNF-α at baseline (P=0.0372) (*Figure 2*). Moreover, TJ-25 was more effective in frequency among the patients with higher levels of IL-8 (P=0.0312). A slight improvement in frequency was discovered in patients with higher baseline MCP-1 levels, but it was not significant (P=0.0652). Improvement in hot flashes with TJ-25 treatment was not linked with any other cytokine or hormone levels. However, ΔTNF-α and ΔIL-8 were not significantly correlated with Δstrength and Δfrequency of hot flashes (*Figure 3*). In addition, the Δstrength or Δfrequency of hot flashes by TJ-25 administration were not significantly associated with Δ values of the other hormonal and cytokine (*Tables 5*,*6*).

Discussion

In the previous prospective study, we showed that TJ-25 was an efficient and safe treatment for hot flashes in PC patients. The strength of hot flashes significantly improved from 4 weeks after TJ-25 administration, and frequency was significantly decreased at the 8-week visit (9). The goal of the current investigation was to clarify the processes underlying the effectiveness of TJ-25 with a particular emphasis on serum cytokine and hormone levels. To our knowledge, this is the first study to examine the relationships of hot flashes with serum cytokine and hormonal levels among PC patients with ADT.

Initially, no significant correlation between VAS and the frequency of hot flashes was not observed, and consequently, the strength and frequency of hot flashes were examined separately in the present analysis, which is likely to be a unique study. We discovered that the strength of hot flashes was inversely associated with estradiol levels, and frequency was inversely correlated with progesterone levels.

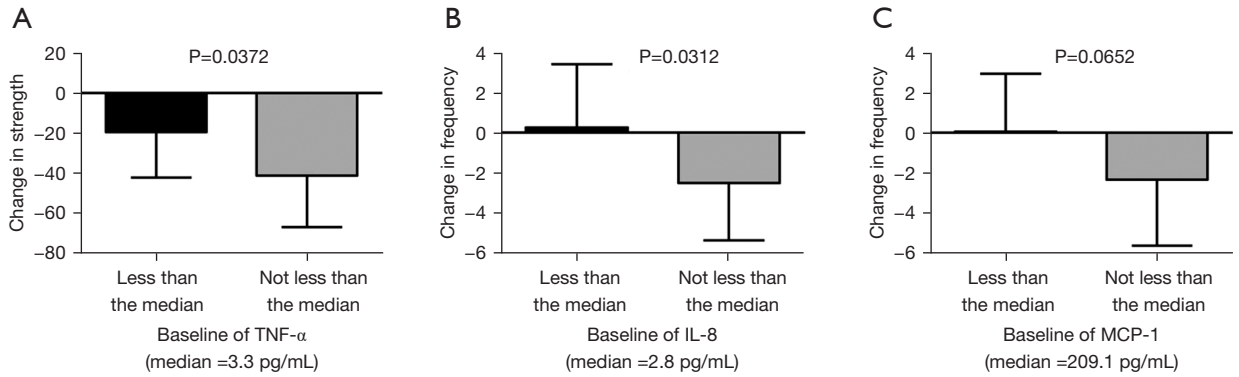

Figure 2 The results of a responder analysis were indicated. (A) Efficacy of TJ-25 for the strength of hot flashes was considerably associated with higher levels of TNF-α at baseline. (B) TJ-25 was more efficient in frequency among the patients with higher levels of IL-8. (C) A slight improvement in frequency was found in patients with higher baseline MCP-1 levels, but it was not significant. TJ-25, keishibukuryogan; INF, tumor necrosis factor; IL, interleukin; MCP, macrophage chemotactic protein-1.

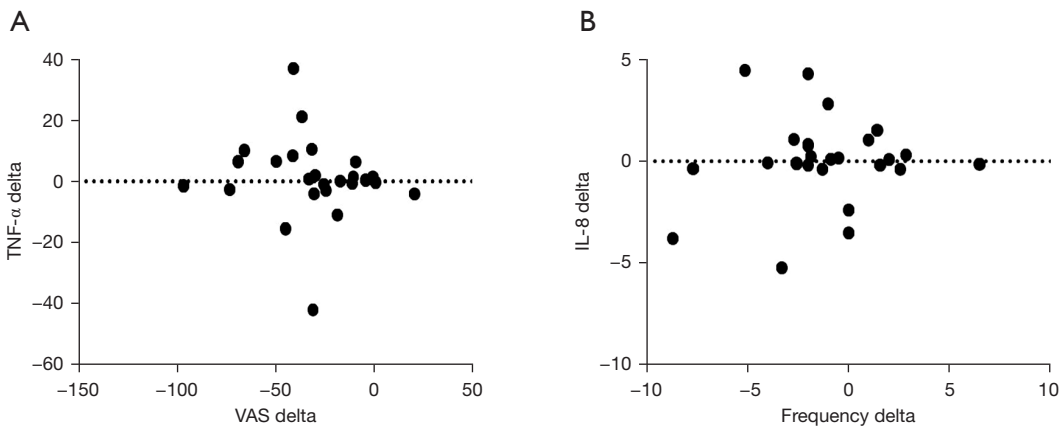

Figure 3 The relationship in change amounts (Δ values) by TJ-25 administration between hot flashes and each parameter was revealed. ΔTNF-α and ΔIL-8 were not significantly associated with Δstrength and Δfrequency of hot flashes. TJ-25, keishibukuryogan; INF, tumor necrosis factor; IL, interleukin.

Table 5 Correlation between each hormone level and the change quantities (Δ values) caused by the injection of TJ-25

	ΔTestosterone	ΔDHEA	ΔDHT	ΔEstradiol	ΔProgesterone
ΔStrength (VAS)					
r	0.071	0.126	0.136	−0.091	0.125
P	0.735	0.548	0.517	0.666	0.553
ΔFrequency					
r	0.253	0.244	0.172	0.152	0.167
P	0.223	0.240	0.412	0.467	0.425

TJ-25, keishibukuryogan; VAS, visual analog scale; DHEA, dehydroepiandrosterone, DHT, dihydrotestosterone.

Table 6 Correlation in change amounts (Δ) by TJ-25 administration between strength/frequency and each cytokine level

	ΔIL-1β	ΔIL-2	ΔIL-4	ΔIL-6	ΔIL-8	ΔIL-10	ΔTNF-α	ΔIFN-γ	ΔMCP-1	ΔMIP-1β	ΔVEGF
ΔStrength (VAS)											
r	0.053	–0.180	–0.138	–0.088	–0.272	–0.138	–0.224	–0.156	–0.213	–0.195	–0.186
p	0.801	0.389	0.512	0.677	0.188	0.509	0.282	0.456	0.307	0.351	0.373
ΔFrequency											
r	0.093	0.015	0.077	0.077	0.015	0.031	0.009	0.026	–0.244	0.038	–0.027
p	0.658	0.945	0.714	0.713	0.942	0.884	0.967	0.903	0.241	0.856	0.900

TJ-25, keishibukuryogan; VAS, visual analogue scale; IFN, interferon; IL, interleukin; MCP, macrophage chemotactic protein; MIP, macrophage inflammatory protein; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Numerous earlier studies have shown that the development of hot flashes in hypogonadal men or male castrated rats is significantly influenced by calcitonin gene-related peptide (CGRP), a powerful vasodilator and a factor in increased regional blood flow (10-15). The decrease in estrogen and progesterone is reported to be associated with the CGRP-induced elevation of skin temperature (13-15). The passed reports explained the upregulation of vessel CGRP receptors in the rats with estrogen and testosterone-deficient rats, and consequently, the skin temperature elevation induced by CGRP injection was significantly greater (15,16). Certain pressures or stimulations may cause the release of CGRP when there is a lack of sex hormones, which could increase the frequency of hot flashes (17). These opinions are likely to support our results that estradiol was importantly correlated with the strength of hot flashes. Furthermore, progesterone inhibited CGRP-induced skin temperature elevation in a dose-dependent manner in the castrated rats (15). Indeed, some placebo-regulated researches have illustrated that medroxyprogesterone alleviated hot flashes in the mail with ADT (5,18). However, mechanisms of how progesterone can affect hot flashes have remained unclear.

On the other hand, no important correlations between hot flashes and any cytokine levels at baseline were observed in the current research, although consistent hot flashes revealed a weak positive correlation with IL-8 levels without a statistical difference. various passed research involving menopausal and postmenopausal women demonstrated that multiple inflammatory cytokines and chemokines, such as IL-6, IL-8, TNF-α, and MIP-1β, also played some significant roles in the improvement of hot flashes, and indicated that hot flashes might be associated with low-grade systemic inflammation (19-21). Particularly, a potential association of IL-8 with hot flashes in women was supported by various passed research (19-21). As with the roles of estrogen in women, it has been widely accepted that testosterone also has some significant roles in the creation and activity of many cytokines in men (22,23). However, our research showed that hot flashes were not importantly correlated with any cytokine levels. For this reason, our researched population was made up of PC patients with ADT, and consequently, the castrated surroundings are likely to be completely different from the menopausal and postmenopausal conditions. Furthermore, the number of subjects included in the current research was extremely limited. There have been currently no passed studies to investigate the link between hot flashes and serum cytokine levels among PC patients with ADT, and further studies involving a large number of subjects need to get to a more definite conclusion.

In the current research, TJ-25 was more efficient in the patients with greater levels of TNF-α for the strength of hot flashes, and IL-8 for consistency, which may also be an interesting finding. Some passed studies targeted to women contributed that the efficacy of TJ-25 was included in circulating cytokine and chemokine levels. TJ-25 has been reported to be reduced inflammatory cytokines and chemokines such as IL-6, IL-8, TNF-α, MCP-1, and MIP-1β (21,24-26). One earlier study found that premenopausal, perimenopausal, and postmenopausal women who received TJ-25 for hot flashes experienced a substantial decrease in blood IL-8 and MCP-1 concentrations in the treatment-responder group (21). We observe significant correlations between baseline serum IL-8 and TNF-α levels, which is likely to be partially consistent with the previous findings. However, there was no correlation between the strength or frequency of hot flashes caused by TJ-25 administration and the levels of these cytokines from baseline to 12-month visits. In particular, ΔIL-8 and ΔTNF-α were not significantly

correlated with Δstrength and Δfrequency of hot flashes. TJ-25's effects, contrary to previous findings (21), were not due to a decrease in these cytokine levels. These findings suggest that TJ-25 does not directly suppress IL-8 and TNF-α production in PC patients with ADT, but it may inhibit some of these cytokines' actions that are associated with the development of hot flashes. However, differences in the relevance of cytokines in the strength and frequency of hot flashes have remained unclear, and further research is expected.

As an alternative mechanism of the effects of TJ-25 on hot flashes, one previous report demonstrated that TJ-25 decreased plasma CGRP levels in postmenopausal women with hot flashes (17). According to one experimental study using human keratinocyte cell lines, CGRP could upregulate IL-8 receptor mRNA expression without increasing IL-8 production (27). This suggests that CGRP suppression may inhibit some IL-8 actions by downregulating its receptor, with no changes in IL-8 as our results indicate. However, there have been no vivo studies to examine the correlation between CGRP and IL-8/IL-8 receptor. Furthermore, because CGRP was not measured in the current study, more research is needed to support this hypothesis.

There are several limitations in the present study that are required to be addressed. To begin with, the number of study subjects is extremely limited. Next, this was a single-arm cross-sectional study with no controls. Furthermore, duration of ADT was not examined in the original study (9), and then a correlation between hot flashes and duration of ADT was not discussed. Duration of ADT may have some effects on cytokine levels. In addition, hot flashes are a subjective reporting of symptoms that can be influenced by many factors such as TJ-25 placebo effects, memory, and other psychological factors. However, this is the first study to examine the efficacy of TJ-25 in men with ADT, focusing on different hormonal and cytokine levels, and it is likely to be a valuable preliminary study. As a result, additional randomized controlled studies involving a sizable number of participants and controls are necessary to verify the findings of this investigation.

Conclusions

The strength of hot flashes was inversely correlated with estradiol levels, and frequency was inversely correlated with progesterone levels. TJ-25 was more effective in patients with higher levels of TNF-α for hot flash strength and IL-8 for frequency, with no significant change in serum levels caused by the treatment. TJ-25 may inhibit some cytokine actions but does not suppress their production.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-121/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-121/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-121/coif). The authors report that this study was supported by specific funding from Tsumura & Co., Tokyo, Japan. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethical Committee of the Kanazawa University Graduate School of Medical Science (No. 2017-214) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants in the study provided written informed consent.

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