



Review Article

Clinical studies investigating the use of leuprorelin for prostate cancer in Asia

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ABSTRACT

Background: Leuprorelin is a well-established treatment for prostate cancer (PCa); however, there is limited information on its use in Asian males. This review of English language publications between January 2000 and 2016 describes the outcomes of clinical trials on leuprorelin in Asian males with PCa of any grade, stage, or histopathology.

Methods: The literature search was undertaken using PubMed, Cochrane Library, and [ClinicalTrials.gov](https://clinicaltrials.gov) databases.

Results: We identified nine studies from Japan, two studies from South Korea, and one international, multisite study which included Asian sites, with a total of 1,652 males previously diagnosed with PCa. All studies included subcutaneous or depot administration of leuprorelin at varying dose levels including 3.75 mg four weekly, 11.25 mg 12 weekly, or 22.5 mg every 12 or 24 weeks. Leuprorelin was administered as monotherapy or in combination with chemotherapy or hormonal therapy. Leuprorelin appears well tolerated in Asian males and is effective in reducing serum testosterone to castration levels (<50 ng/dL (<1.7 nmol/L)) and prostate-specific antigen levels. Common adverse events included hot flushes and mild hepatic dysfunction. Leuprorelin was shown to provide reasonable survival rates in PCa (T1b-T3N0M0) and in metastatic disease; another reasonable option for these patients is radiation therapy. Leuprorelin treatment also improved the quality of life.

Conclusion: Leuprorelin may be an appropriate and efficacious treatment for males with PCa (T1b-T3N0M0). Leuprorelin treatment was well tolerated and associated with improvement in the quality of life.

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1. Background

The burden of prostate cancer (PCa) is well established internationally: PCa has the highest morbidity and second highest mortality rate after lung cancer in European and American males.¹ Incidence rates of PCa are generally low in Asian countries but have continued growing over recent years,^{1–3} and PCa was the second most reported cancer in Japan in 2011.³

Leuprorelin, also known as leuprolide, is a synthetic analogue of naturally occurring gonadotropin-releasing hormone (GnRH), a potent inhibitor of gonadotropin secretion when administered

continuously.⁴ After an initial increase, continuous administration decreases levels of luteinizing hormone (LH) and follicle-stimulating hormones, and in males, testosterone is reduced to below castrate threshold (≤ 50 ng/dL).⁴ Other GnRH agonists developed and marketed for PCa include goserelin, triptorelin, and histrelin.

Open-label, multicenter, clinical studies on males with advanced PCa investigated multiple dosing intervals and demonstrated achievement and maintenance of serum testosterone suppression over 6 months (1 and 3-monthly dosing schedules), 8 months (4 monthly dosing schedule), and 12 months (6-monthly dosing schedule).⁴ At all dosing levels, leuprorelin achieved castrate threshold (≤ 50 ng/dL) within 2–6 weeks of treatment initiation, with reversible effects upon discontinuation.⁴ Leuprorelin is contraindicated in patients who underwent orchiectomy as it does not further reduce serum testosterone.⁴

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Table 1
Study characteristics: efficacy results^{1–12}

Attribute	Leuprorelin (L) 3.75 mg, 4 weekly ^{1–3} 5, 7, 8, 12	Leuprorelin 3.75 mg, once only ^{4, 11}	Leuprorelin 11.25 mg, 3 monthly ¹⁰	Leuprorelin 22.5 mg, 3 monthly ^{6, 9}	Leuprorelin 22.5 mg, 6 monthly ¹⁰	Goserelin 3.6 mg, once only ¹¹	Leuprorelin + chlormadinone acetate 100 mg daily ^{1–3, 7, 12}	Leuprorelin + diethylstilbestrol diphosphate 300 mg daily ¹²	Leuprorelin+ docetaxel 75 mg/m ² , 3 weekly for 18 months ⁹	Leuprorelin+ flutamide 375 mg, daily, for 36 weeks ⁵ ; flutamide administered on Day 0 or 1, 2, or 4 weeks before leuprorelin ⁴	Leuprorelin+ bicalutamide 80 mg daily ⁷
Serum levels											
Testosterone											
Baseline testosterone level (ng/dL), mean	460 (±160) ² 405.1 T3NOM0 447.1 (T2-3N1M0, T4NOM0, T2-3NOM1) ⁸ 538 (±283) ¹²	364.5 (117.3) ¹¹ Group A: 500 (370–630) ⁴	9.1 (±8.5) ¹⁰	–	13.3 (±43.5) ¹⁰	398.6 (131.9) ¹¹	500 (±270) ² 435 (±127) ¹²	348 (±135) ¹²	–	Group B: 104.4 (23.5–189.1) Group C: 151.1 (19.9–625.4) Group D: 68.3 (22.1–206.7) Group E: 56.3 (17.5–89.0) ⁴ 405.1 T3NOM0 447.1 T2-T3 N1M0, T4NOM0, T2-T3NOM1 ⁸	–
Posttreatment testosterone levels (ng/dL)	–	Group A: 31 (±16) at Day 28 ⁴	–	–	–	–	100, after administration ¹²	11.4, after administration ¹²	–	Group B: 36 (±37) Group C: 12 (±4) Group D: 46 (±40) Group E: 15 (±6) at Day 28398. ⁴	–
Achieved castrate levels of testosterone (%) ^a ≤ 50 ng/dL; ^b ≤ 100 ng/dL	97.8% (87 of 89) by w4 ^{5, a}	90.90% (10 of 11) by Day 28 ^{11, a}	98.7% (78 of 79) throughout 48 weeks (FAS) ^{10, a}	100% (n = 42) by w4, 15.6 (mean); 8.4 at w24 ^{6, a}	98.8% (80 of 81) throughout 48 weeks (FAS) ^{10, a}	100% (n = 11) by Day 28 ^{11, a}	–	–	–	–	–
Testosterone recovery, days (95% CI)	–	–	–	535 (95% CI: 457, 749) ⁹	–	–	–	–	458 days (95% CI: 336, 529 days) ⁹	–	–
Prostate-specific antigen (PSA)											
Baseline PSA (ng/mL)	52.4 (±103.5) ¹ 41.2 (±84.0) (0.2–620) ² 43.8 (±111.9) (p < 0.05) ³ 60.3 (4.2–450) T3NOM0 64.9 (6.0–370) (T2-3N1M0, T4NOM0, T2-3NOM1) ⁸ 83.6 (±98.1) ¹²	Group A: 79.6 (18.7–191.1) ⁴ 49.3 (59.4) (n = 11) ¹¹	0.0220 (median) ¹⁰	67.9 (130.8) ⁶	0.0300, before treatment (median) ¹⁰	23.6 (19.2) ¹¹	151.5 (±742.4) ¹ 46.5 (±136.5) (0.2–1200) ² 103.6 (±539.1) (p < 0.05) ³ 103.7 (±171.1) ⁷ 520.9 (±1793.3) ¹²	212.3 (±458.3) ¹²	–	60.3 (4.2–450) T3NOM0 64.9 (6.0–370) T2-T3 N1M0, T4NOM0, T2-T3NOM1 ⁸ Group B: 104.4 (23.5–189.1) Group C: 151.1 (19.9–625.4) Group D: 68.3 (22.1–206.7) Group E: 56.3 (17.5–89.0) ⁴	135.4 (±476.0) ⁷
Endpoint PSA (ng/mL)	–	79.6 (±59.9), posttreatment Day 0; 83.4 (±66.6), Day 7; 41.8 (±51.7), Day 28 ⁴	0.0095 at 24 weeks (median) 0.0000 ng/ml at 48 weeks (median) ¹⁰	3.0 by w24 (total cohort n = 42) ⁶	0.0130 at 24 weeks (median); 0.0000 ng/ml at 48 weeks (median) ¹⁰	–	–	–	–	Posttreatment, Day 0: Group B: 104.4 (±78.1) Group C: 73.6 (±125.4), Group D: 25.1 (±38.9), Group E: 10.1 (±6.6), Day 7 Group B: 53.2 (±39.4), Group C: 53.6 (±98.7), Group D: 29.8 (±49.6), Group E: 9.6 (±5.7), Day 28 Group B: 9.9 (±8.4) Group C: 15.6 (±30.0) Group D: 3.5 (±5.7) Group E: 2.4 (±2.3) ⁴	–

Treatment outcomes	68% at 5 yrs (n = 151) ³	87% (T1b, T1c); 57% (T2a); 91% (T2b); and 70% (T3) (n = 78) at 2 yrs ¹	49.3% CR at w12 (n = 78) ¹	49.3% at w12 (n = 78) ¹	Underpowered to detect differences ⁹	Underpowered to detect differences ⁹
Overall survival (OS)	87% at 5 yrs (n = 176) ³	87% (T1b, T1c); 66% (T2a); 62% (T2b); and 43% (T3) (n = 73) at 2 yrs ¹	49.3% CR at w12 (n = 73) (1)	50.7% at w12 (n = 73) ¹		
Progression-free survival (PFS)						
Response: complete response (CR)						9.09% PD (10 of 110 immediate treatment) at 3.4 years (2.3–3.8) (9)
partial response (PR)						7.3% PD (9 of 118 deferred treatment) at 3.4 years (2.3–3.8) ⁹
progressive disease (PD)						

AE, adverse event; CAB, combined androgen blockade; CR, complete response; CTC/AE, Common Terminology Criteria for Adverse Events; GnRH, gonadotropin-releasing hormone; IV, intravenous; MAB, maximal androgen blockade; NS, not statistically significant; OS, overall survival; PD, progressive disease; PR, partial response; PFS, progression-free survival; PO, oral; PSA, prostate-specific antigen; RP, radical prostatectomy; SAE, serious adverse event; SC, subcutaneous; SR, slow release; QOL, quality of life; 6M, 6 monthly; 3M, 3 monthly.

While first approved for PCA, leuprorelin has also been approved internationally for treatment of premenopausal breast cancer, central precocious puberty, and endometriosis and can be administered every 4, 12, or 24 weeks. Leuprorelin is approved for treatment of PCA and premenopausal breast cancer in Japan;⁵ for treatment of PCA, premenopausal breast cancer, fibroids, and central precocious puberty in the United States;⁶ and for treatment of endometriosis, premenopausal breast cancer, hypermenorrhea, and central precocious puberty in Korea.⁷

This article reviews outcomes from clinical studies where leuprorelin was administered for PCA of any grade, stage, or histopathology in Asia. Articles searched were published in English between January 2000 and 2016 in journals indexed in PubMed, from the Cochrane Library or from reports in ClinicalTrials.org.

1.1. Clinical trials of leuprorelin

Twelve articles were selected from an initial 430, after removing duplicates and those not meeting inclusion criteria. Efficacy and safety of leuprorelin from included clinical studies are shown in [Tables 1 and 2](#), and quality of life (QOL) is shown in [Table 3](#).

Of the 12 studies in this review, 9 were conducted in Japan,^{1, 3, 8–14} two were conducted in South Korea,^{2, 15} and one was an international, multicenter study, with two sites in Asia.¹⁶ A total of 1,652 males with a previous diagnosis of PCA were included in the studies (study range: 26–402), and study durations ranged from 4 weeks to 5 years. All studies included subcutaneous or depot administration of leuprorelin at varying dose levels including 22.5 mg at either 3-^{15, 16} or 6-monthly³ intervals, 11.25 mg 3 monthly³, or 3.75 mg every 28 days.^{1, 2, 8–14} Leuprorelin was administered either as a monotherapy^{2, 3, 12, 15} or with adjuvant chemotherapy¹⁶ or antiandrogen therapy.^{1, 8–11, 13, 14}

1.2. Effects of leuprorelin on prostate-specific antigen and testosterone serum levels

Seven studies examined leuprorelin on serum prostate-specific antigen (PSA) and/or testosterone levels.^{1–3, 10–12, 15} Suzuki *et al.*³ compared depot 6-monthly (22.5 mg) to depot 3-monthly (11.25 mg) and established that the 6-monthly regimen was non-inferior to the 3-monthly regimen for the suppressive effect on serum testosterone in patients with \geq T1b and any nodal involvement or metastatic classification. Estimated between-group difference in suppression rates was 1.3% [two-sided 95% confidence interval (CI), 3.4–6.8].³ The suppression rate of serum testosterone at \leq 50 ng/dL throughout 48 weeks was 98.8% (80 of 81) in the 6-monthly group and 98.7% (78 of 79) in the 3-monthly group; estimated between-group difference in rates was 0.0% (two-sided 95% CI, –5.5–5.7).³ The median PSA concentration before treatment was 0.0300 ng/mL in the 6-monthly group and 0.0220 ng/mL in the 3-monthly group (patients had previously used leuprorelin 3 monthly continuously, excluding neoadjuvant therapy, for a period of 24–96 weeks, and nonsteroidal antiandrogen for \geq 12 weeks continuously if taking any); by week 48, the median PSA level in both groups was 0.00 ng/mL.³ Serum testosterone levels were maintained throughout at $<$ 100 ng/dL (the standard castration level is now \leq 50 ng/dL); median serum testosterone levels before treatment (as per above criteria) were 8.0 ng/dL and 7.0 ng/dL in the 6-monthly and 3-monthly groups, respectively; at week 48, median testosterone serum levels were 9.0 ng/dL (6-monthly groups) and 6.0 ng/dL (3-monthly groups).³

In a single-arm study on patients with histologically confirmed PCA, all (n = 42) participants treated with depot leuprorelin 22.5 mg 3 monthly reached serum testosterone castration range by Week 4 (mean 15.6 ng/dL), and one patient experienced a

Table 2
Study characteristics: AEs^{1–3, 5, 6, 8–10, 12}

Attribute	Leuprorelin 3.75 mg, 4 weekly ^{5, 8, 12}	Leuprorelin 11.25 mg, 3 monthly ¹⁰	Leuprorelin 22.5 mg, 3 monthly ⁶	Leuprorelin 22.5 mg, 6 monthly ¹⁰	Chlormadinone acetate 100 mg daily ¹²	Diethylstilbestrol diphosphate 300 mg daily ¹²	Flutamide 375 mg, daily, PO for 36 weeks ⁸
Serum levels							
Transient increase in alanine/aspartate transaminase levels	19.2% (n = 66) ⁵	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Transaminase glutamic oxaloacetic transaminase or glutamic pyruvic transaminase	1 (n = 17) (GOT) and 1 (n = 17) (GOT) ^{a 12}	Not reported	Not reported	Not reported	1 (n = 17) (GOT) and 1 (n = 17) (GOT) ^{a 12}	Not reported	17% (8 of 47) ⁸
Anemia	13.5% (n = 66) ⁵	Not reported	Not reported	Not reported	Not reported	5 (n = 19) ^{a 12}	Not reported
Febrile neutropenia	13.5% (n = 66) ⁵	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Treatment-related symptoms							
Hot flashes	1.5% (n = 66) ⁵	6.3 (n = 79) ^{b 10}	20% (n = 4) ^{c 6}	6.2 (n = 81) ^{b 10}	Not reported	Not reported	Not reported
Sweating	Not reported	Not reported	Not reported	Not reported	Not reported	1 (n = 19) ^{a 12}	Not reported
Condition-related symptoms							
Pain	Not reported	Not reported	10% (n = 2) ^{c 6}	Not reported	Not reported	Not reported	Not reported
Infection							
Nasopharyngitis	Not reported	Not reported	10% (n = 2) ^{c 6}	Not reported	Not reported	Not reported	Not reported
Other							
Pulmonary infarction	Not reported	Not reported	Not reported	1.23% (1 patient) (n = 81) ^{b 10}	Not reported	Not reported	Not reported
Cerebral infarction	Not reported	Not reported	Not reported	1.23% (1 patient) (n = 81) ^{b 10}	Not reported	Not reported	Not reported
Peripheral arterial occlusive disease	Not reported	1.2% (1 patient) (n = 79) ^{b 10}	Not reported	Not reported	Not reported	Not reported	Not reported
Heart failure	Not reported	Not reported	Not reported	Not reported	Not reported	1 (n = 19) ^{a 12}	Not reported

Notes: Sakai *et al.*, Tanaka *et al.*, and Tsushima *et al.* did not report AE data. Akaza *et al.* reported that “23 patients in Group I and 21 in Group II showed various AE drug reactions such as an elevation of serum transaminase level, feeling hot, or fatigue, but there were no SAE drug reactions”; no additional data were provided. In both articles by Homma *et al.*, two discontinuations related to drug-related AEs were reported; however, no details were provided regarding from what treatment arms. Schweitzer *et al.* reported 86% of patients experienced at least 1 AE, the majority of which were Grade 1 or 2; Grade 3 and 4 AEs were reported in 21 patients, the most common being febrile neutropenia (23.8%); however, the treatment arm was not stated.

AE, adverse event; CAB, combined androgen blockade; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; GnRH, gonadotropin-releasing hormone; IV, intravenous; MAB, maximal androgen blockade; NS, not statistically significant; OS, overall survival; PFS, progression-free survival; PO, oral; PSA, prostate-specific antigen; RP, radical prostatectomy; SAE, serious adverse event; SC, subcutaneous; SR, slow release; QOL, quality of life; 6M, 6 monthly; 3M, 3 monthly.

^{a)} Reported as the number of events and the number of patients reported effected by event in parentheses.

^{b)} Reported as the percentage of patients experiencing AE and the number of patients in the study arm in parentheses.

^{c)} Percentage is based on the number of patients reporting AE and not the total number of patients in the study.

breakthrough response by Week 8; however, all participants were medically castrated by Week 12 and maintained up to 24 weeks (mean, 8.4 ng/dL).¹⁵ The mean [standard deviation (SD); min to max] PSA level at baseline for all ($n = 42$) participants was 67.9 ng/mL (± 130.80 ; 0.31–579.00); by Week 24, the mean was 3.0 ng/mL. There were no significant PSA or testosterone changes according to clinical stage or body mass index,¹⁵ and despite sexual function decreasing, leuprorelin at this regimen is effective in Asian populations.¹⁵

In patients with localized and locally advanced PCa (T1b, T1c, T2b, or T3a) who were not scheduled for radical prostatectomy (RP), Akaza *et al.*¹⁰ found a wide pretreatment range of PSA levels. Owing to a large SD in PSA levels in the leuprorelin/chlormadinone combination arm (151.5 ng/mL \pm 742.4; range, 0.8–6,350 ng/mL) compared with the monotherapy arm (52.4 ng/mL \pm 103.5; range, 0.6–711 ng/mL), a statistical analysis between arms was unfeasible.¹⁰ Patients with baseline serum testosterone of at least 1 ng/mL were eligible for study participation; no further serum testosterone levels were reported.¹⁰

Tsushima *et al.*¹ reported that mean PSA levels were increased beyond pretreatment levels in participants not pretreated with flutamide and that mean PSA levels did not exceed pretreatment levels after leuprorelin administration in participants pretreated with flutamide. Serum testosterone levels were increased in participants pretreated with flutamide; however, compared across all treatment groups, the testosterone surge after leuprorelin administration was similar.¹ These results indicate that flutamide inhibits the influence of a testosterone surge after leuprorelin administration, and simultaneous administration of flutamide is sufficient to suppress the flare-up phenomena.¹

By Week 4, 97.8% (87 of 89) of participants in the prospective, single-arm study by You *et al.*² had achieved a serum testosterone level within castration range; medical castration was achieved and maintained in 96.6% (86 of 89) of participants.

Tanaka *et al.*¹² compared the effect of subcutaneous leuprorelin (3.75 mg) with subcutaneous goserelin (3.6 mg) on serum levels of free and total testosterone, LH, and PSA levels. PSA levels began to decrease in both treatment groups from Day 14, and total and free testosterone concentrations increased transiently relative to baseline, over the first 7 days.¹² The mean rate of change was significantly greater in the leuprorelin arm than in the goserelin arm for total testosterone level at Day 3 ($p = 0.0278$, SD not reported) and free testosterone ($p = 0.027$ and $p = 0.0452$, SDs not reported) concentrations at Day 3 and 7, respectively.¹²

Ohuchi *et al.*¹¹ demonstrated that PSA levels declined early in participants pretreated with either chlormadinone acetate (CMA) or diethylstilbestrol diphosphate (DES-P) ($p < 0.01$); no remarkable changes were seen after leuprorelin administration.¹¹ After initially elevating from baseline on Day 2, serum testosterone decreased in leuprorelin monotherapy arms.¹¹ In participants pretreated with DES-P, serum testosterone levels decreased from 338 ng/dL to 11.4 ng/dL ($p < 0.01$), and CMA from 447 ng/dL to 100 ng/dL [$p < 0.01$, SD not reported].¹¹ After serum testosterone levels initially increased on Day 2 after leuprorelin administration, serum levels decreased to castrate levels by Week 2.¹¹ In both DES-P and CMA treatment arms, there was a small testosterone flare-up; however, at its peak, it did not exceed the pretreatment baseline.¹¹

1.3. Progression-free and overall survival

Homma *et al.*⁹ demonstrated no significant difference in 5-year outcomes [overall survival (OS), cause-specific survival, clinical relapse-free survival, or PSA relapse-free survival] in participants who underwent RP and adjuvant endocrine therapy compared with those undergoing preoperative androgen deprivation. The

pretreatment group was at significantly higher risk of organ-confined disease (OCD) than those receiving preoperative treatment [odds ratio (OR), 2.44; 95% CI, 1.04–5.72; $p < 0.04$].⁹ The presence of OCD ($n = 29$) correlated with a significant difference in favor of cause-specific survival, progression-free survival (PFS) and PSA relapse-free survival.⁹

Akaza *et al.*¹⁰ reported improved PFS ($p < 0.05$) in participants who received combination treatment with leuprorelin and CMA when compared with leuprorelin monotherapy ($p = 0.0242$). The two-year PFS rates for participants with T2b PCa was 62% in the monotherapy arm ($n = 20$) and 43% in the combination therapy arm ($n = 16$) ($p = 0.0175$); participants with T3 PCa had a PFS of 91% ($n = 31$) and 73% ($n = 37$) ($p = 0.0316$), respectively.¹⁰

In a study by Schweizer *et al.*¹⁶ patients (1:1:1) with high-risk PCa after RP were randomized to adjuvant leuprolide with or without docetaxel either immediately after RP or deferred until disease progression. After a median follow-up of 3.4 years (interquartile range, 2.3–3.8), Schweizer *et al.*¹⁶ reported that 17% (41 of 228) of participants had disease progression; 22% (24 of 110) of participants in the immediate treatment (14 in the hormone therapy-alone arm and 10 in the hormone therapy with chemotherapy arm) group had disease progression compared with 14% (17 of 118) in the deferred group (8 in the hormone therapy-alone arm and 9 in the hormone therapy with chemotherapy arm).¹⁶ The study was underpowered to detect significant differences between study arms or all endpoints.¹⁶

1.4. Antitumor effects

Akaza *et al.*¹⁰ compared the antitumor effect of leuprorelin (3.75 mg monthly) with leuprorelin at the same dose in combination with CMA (100 mg daily). Antitumor effects were evaluated according to PSA criteria.¹⁰ Results indicated that at 2 years, complete response was seen in 61.8% (21 of 34) and 67.6% (23 of 34) of participants in monotherapy and combination arms, respectively, indicating that early endocrine therapy is reasonable for patients with localized or locally advanced PCa where RP is not planned.¹⁰

1.5. Quality of Life

Three studies^{2, 13, 14} considered the impact of leuprorelin therapy on QOL measures (Table 3). Sakai *et al.*¹³ randomized participants to receive combined androgen blockade (CAB) using leuprorelin in combination with CMA (a steroidal antiandrogen) or bicalutamide (a nonsteroidal antiandrogen); data were available for 124 participants. The incidence, frequency, and distress caused by hot flushes were self-reported over a two-year period using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. A significant difference was noted in its timing; those treated with chlormadinone in combination with CAB experienced warmth/flushing and sweating more often while sleeping (24.7% and 7.4%, respectively, $p < 0.001$), and those treated with bicalutamide experienced these symptoms when feeling tense (18.9% and 91%, respectively, $p < 0.001$).¹³ Although no significant difference was seen in the frequency of warmth/flushing episodes between groups [1.3 (1.0–3.4) and 2.2 (1.1–5.0) episodes per day, respectively, $p = 0.16$], the median frequency of sweating was lower in the chlormadinone arm than in the bicalutamide arm [1.0 (0.8–3.3) and 3.6 (2.2–5.2) episodes per day, respectively, $p = 0.21$].¹³ Discontent levels regarding warmth/hot flushes (OR, 0.47; $p < 0.001$) and sweating (OR, 0.61; $p = 0.1$) were significantly lower in the chlormadinone arm. During the treatment period, the incidence of warmth/flushing and sweating was lower in the chlormadinone arm than in the bicalutamide arm (warmth/flushing:

Table 3
Study characteristics: QOL^{5, 7, 8}

Attribute	Leuprorelin 3.75 mg, 4 weekly ^{5, 7, 8}	Flutamide 375 mg, daily, PO for 36 weeks ⁸	Chlormadinone 100 mg, daily ⁷	Bicalutamide 80 mg, daily ⁷
Treatment-related symptoms				
Hot flashes	5.3 (±1.4) at baseline and 23.6 (±2.8) ^a at 12 weeks (p < 0.001) ⁵	Not reported	Not reported	Not reported
Sweating (episodes/d), frequency	Not reported	Not reported	1.0 (0.8–3.3) p = 0.021 ^{b 7}	3.6 (2.2–6.2) p = 0.021 ^{b 7}
Discontent			14 patients (2.5%) p = 0.027 ⁷	29 patients (4.4%) p = 0.027 ⁷
Warmth and flushing (episodes/d), frequency	Not reported	Not reported	1.3 (1.0–3.4) p = 0.16 ^{b 7}	2.2 (1.1–5.0) p = 0.16 ^{b 7}
Discontent			19 patients (3.3%) p < 0.001 ⁷	41 patients (5.6%) p < 0.001 ⁷
Urinary symptoms				
Daytime frequency	42.5 (±2.7) at baseline and 34.0 (±2.4) at 12 weeks (p = 0.004) ⁵	Not reported	Not reported	Not reported
Sexual functioning				
Erection problems	38.1 (±3.6) at baseline and 49.8 (±4.0) ^a at 12 weeks (p = 0.030) ⁵	Not reported	Not reported	Not reported
Uncomfortable sexual intimacy	24.2 (±2.9) at baseline and 37.6 (±4.0) ^a at Week 12 (p = 0.023) ⁵	Not reported	Not reported	Not reported
Potency	Not reported	14.7 before treatment and 2.4 after MAB for 36 weeks (n = 13) (p < 0.001) ^c . In the off-treatment period, the mean potency score increased to 11.4 (p < 0.001) ⁸ .	Not reported	Not reported
Global health status/QOL				
	Reported as at baseline and at Week 12			
	54.7 (±2.2), 63.4 (±2.3); p < 0.001 ^{a 5}	Reported as before treatment, on treatment, and off treatment	Not reported	Not reported
Functional scales				
Physical	83.2 (±1.7), 79.0 (±2.0); p = 0.012 ⁵	25.1, 2.4, 11.4; p < 0.01 ⁸	Not reported	Not reported
Role	85.1 (±1.9), 79.9 (±2.2); p = 0.007 ⁵	Not reported		
Emotional	79.7 (±2.1), 84.2 (±1.7); p = 0.082 ⁵	18.4, 19.5, 19.0; NS ⁸		
Cognitive	80.7 (±1.9), 81.4 (±1.6); p = 0.862 ⁵	Not reported		
Social	80.2 (±2.2), 81.1 (±2.2); p = 0.902 ⁵	16.5, 16.1, 20.3; p < 0.001 ⁸		
Symptom scales/items				
Fatigue	28.0 (±2.0), 29.1 (±2.1); p = 0.709 ⁵	3.4, 2.7, 3.6; <0.05 (before vs on treatment) and <0.01 (on vs off treatment) NB: reported as lack of energy ⁸	Not reported	Not reported
Appetite loss	16.4 (±2.5), 9.4 (±1.7); p = 0.003 ⁵	Not reported		

Notes: Akaza *et al.*, Homma *et al.*, Homma *et al.*, Lee *et al.*, Ohuchi *et al.*, Schweitzer *et al.*, Suzuki *et al.*, Tanaka *et al.*, and Tsushima *et al.* did not report QOL data.

AE, adverse event; CAB, combined androgen blockade; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-PR25, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Prostate Specific 25-item; FACT-G, Functional Assessment of Cancer Therapy – General; GnRH, gonadotropin-releasing hormone; IV, intravenous; MAB, maximal androgen blockade; NS, not statistically significant; OS, overall survival; PFS, progression-free survival; PO, oral; PSA, prostate-specific antigen; QOL, quality of life; RP, radical prostatectomy; SAE, serious adverse event; SC, subcutaneous; SR, slow release; 6M, 6 monthly; 3M, 3 monthly.

^{a)} Data shown as mean (SD), measured using the EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires.

^{b)} Data presented as median, with interquartile range in parentheses.

^{c)} Data presented as mean, measured using the FACT-G and the abridged 5-item International Index of Erectile Function.

43.3% and 51.4%, respectively, $p = 0.51$; sweating: 51.7% and 48.5%, respectively, $p = 0.80$).¹³

Using the FACT – General (FACT-G) QOL questionnaire, Sato *et al.*¹⁴ demonstrated that participants treated with combined leuprorelin and flutamide had improved QOL outcomes during off-treatment periods when compared with on-treatment periods. Significant differences in QOL outcomes were seen in potency and physical well-being, where worse scores were recorded during on-treatment periods than during off-treatment periods. QOL scores for potency during on-treatment and off-treatment periods were significant (2.4 and 11.4, respectively, $p < 0.01$), as was physical well-being when on-treatment scores were compared with off-treatment scores (3.3 and 3.8, respectively, $p < 0.05$).¹⁴ Other significant changes were social/family well-being (16.1 and 20.3, respectively, $p < 0.01$) and functional well-being (“I am able to enjoy life”; 3.1 and 3.6, respectively, $p < 0.05$).¹⁴

You *et al.*² reviewed the role of leuprorelin in improving QOL in South Korean males with PCA. Participants received three, once-monthly doses of subcutaneous leuprorelin (3.75 mg); 89 of 104 participants completed the 12-week, open-label study. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the PCA-specific module (QLQ-PR25) were used to assess QOL measures in patients before treatment and at 12 weeks. Results indicated a significant ($p < 0.001$) improvement in global health status/QOL based on responses to the EORTC QLQ-C30 questionnaire. A significant ($p < 0.001$) improvement was seen in global health from baseline (54.7 ± 2.2) and at Week 12 (63.4 ± 2.3); however, deteriorations occurred in physical and role functioning and a small, nonclinically relevant improvement was seen in emotional functioning.² A significant improvement was seen in symptom scales for appetite from baseline compared with Week 12 (16.4 ± 2.5 and 9.4 ± 1.7 , respectively, $p = 0.003$).² Specific to the QLQ-PR25 module, a significant ($p = 0.004$) improvement was seen in daytime urinary frequency from baseline (42.5 ± 2.7) to Week 12 (34.0 ± 2.4).² Significant increases from baseline to Week 12 were seen in treatment-related symptoms such as hot flushes (5.3 ± 1.4 and 23.6 ± 2.8 , respectively, $p < 0.001$). In addition, a significant increase in erection problems (31.8 ± 3.6 and 49.8 ± 4.0 , $p = 0.030$) and uncomfortable sexual intimacy (24.2 ± 2.9 and 37.6 ± 4.0 , $p = 0.023$) was observed between baseline and Week 12.² You *et al.*² concluded that while treatment with leuprorelin decreased physical and role functioning, there was improvement in global health status/QOL and emotional functioning. Furthermore, they noted that while treatment led to increases in hot flushes and erection problems, it also caused a decrease in urinary symptoms and increase in appetite.

1.6. Adverse effects

Eight studies^{1–3, 11, 13–16} reported adverse events (AEs) associated with leuprorelin monotherapy or in combination with other treatments. The most commonly observed AEs were hot flushes,^{8, 13} nasopharyngitis,³ febrile neutropenia,¹⁶ and abnormal hepatic function.¹ Suzuki *et al.*³ reported AEs in 92.6% (75 of 81) and 89.9% (71 of 79) of participants treated with leuprorelin on the 6-monthly and 3-monthly regimens, respectively. The most common AE nasopharyngitis was seen in 22.2% ($n = 18$) of participants in the 6-monthly regimen and 31.6% ($n = 25$) of participants in the 3-monthly regimen; however, it was noted that most AEs were considered unrelated to leuprorelin treatment.³ AEs leading to study discontinuation were reported in 2.5% ($n = 2$) of participants in the 6-monthly treatment group and 3.8% ($n = 3$) of participants in the 3-monthly group.³ Serious AEs (SAEs) were reported in 12.3% ($n = 10$) and 10.1% ($n = 8$) of participants in the 6-monthly and 3-

monthly treatment groups, respectively.³ One case of pulmonary infarct and one cerebral infarct were reported in the 6-monthly treatment group, and one event of peripheral arterial occlusive disease was reported in the 3-monthly group.³ One death, not related to leuprorelin, was reported in the 6-monthly group.³

Fifteen participants (35.7%) reported 20 AEs in the study by Lee *et al.*¹⁵ ($n = 42$). Hot flushes of mild intensity ($n = 4$, 20%) were the most common AE, followed by pain ($n = 2$, 10%) and infection ($n = 2$, 10%).¹⁵ No participants withdrew from the study because of AEs.¹⁵

In the study by Schweizer *et al.*,¹⁶ 86% (118 of 138) of participants who received treatment reported a least one AE which was considered possibly drug related. AEs were similar to treatments administered as monotherapies; most were of common toxicity criteria Grade 1 or 2. Twenty-one (15%) Grade 3 or 4 AEs were reported; these occurred more frequently in participants who received chemotherapy, with the most common being febrile neutropenia ($n = 5$, 23.8%).¹⁶

Tsushima *et al.*¹ reported a dull headache in the leuprorelin monotherapy arm ($n = 6$).¹ Grade 1 abnormal hepatic function was observed in 40% (8 of 20) of patients treated with the combination treatment of leuprorelin and flutamide; although one participant had a one-week treatment withdrawal period, the administration of flutamide was not ceased in any participant.¹

You *et al.*² observed a total of 126 AEs in 66 participants (63.5%, study $n = 104$).² Regardless of causality, transient increased alanine/aspartate transaminase levels (19.2%), azotemia (13.5%), and anemia (13.5%) were the most common AEs reported.² One participant suffered Grade 3 hot flushes resulting in study withdrawal; other AEs reported were of mild intensity.²

Twenty-one of 55 participants in the study by Ohuchi *et al.*¹¹ reported AEs; 13 were seen in the leuprorelin/DES-P combination arm ($n = 19$).¹¹ No SAEs were reported, and no side effects attributable to flare-up were observed in any treatment group.¹¹

Elevated serum transaminase glutamic oxaloacetic transaminase or glutamic pyruvic transaminase was reported in 17% (8 of 47) of participants in the study by Sato *et al.*¹⁴ and was suspected to be an AE associated with flutamide. Three participants were managed with a flutamide dose reduction, and 5 were switched to CMA; no further AEs were observed in these participants.¹⁴

Sakai *et al.*¹³ demonstrated a significant difference in the timing of hot flushes associated between the 2 treatment groups ($p < 0.001$) and concluded that CAB with a steroidal antiandrogen may induce fewer and less-distressing hot flushes.¹³ Furthermore, 13.3% ($n = 8$) of participants had Grade 2 or higher toxicities for hepatic dysfunction in the chlormadinone group, and 3.1% ($n = 2$) reported diarrhea and 3.1% ($n = 2$) reported anemia in the bicalutamide group.¹³

2. Discussion

Several studies examined the effects of leuprorelin on serum PSA and/or testosterone levels.^{1–3, 10–12, 15} Results indicated that administration of 22.5 mg was effective in producing and maintaining castration levels (≤ 100 ng/dL³; ≤ 50 ng/dL¹⁵) of testosterone over a 6-month period^{3, 15} and it was demonstrated to be non-inferior to 11.25 mg of leuprorelin 3 monthly in suppressing serum testosterone levels.³ Treatment with 3.75 mg (4 weekly) of leuprorelin was shown to rapidly achieve serum testosterone levels within castration range (≤ 50 ng/dL) after 4 weeks.² While there was a reported decrease in sexual function, leuprorelin 22.5 mg depot 3-monthly was effective in maintaining castration levels of serum testosterone in Asian participants with PCA.¹⁵

When used in combination with CMA, leuprorelin had longer PFS than in those treated with monotherapy.¹⁰ At 5 years,

preoperative androgen deprivation therapy (ADT) with leuporelin and CMA failed to display a benefit in participants undergoing RP and endocrine therapy.⁸ The probability of OCD was associated with no clinical relapse during the follow-up period.⁸ In a subsequent study, leuporelin as either monotherapy or in CAB offered a reasonable survival rate for participants with T1b-T3N0M0 PCa within a 5-year follow-up period.⁹

Pretreatment either with DES-P (300 mg) or CMA (100 mg) 2 weeks before commencing subcutaneous leuporelin (3.75 mg 4 weekly) was effective in preventing disease flare-up associated with the first administration of leuporelin.¹¹ In addition, participants pretreated with oral flutamide (375 mg daily) before commencing leuporelin demonstrated that flutamide prevented postleuporelin treatment flare-up,¹ impacting QOL. Furthermore, a greater initial surge in testosterone was observed in patients treated with leuporelin (3.75 mg) than with goserelin (3.6 mg); the LH surge and low incidence of tumor flare-up reactions were similar in both treatment arms.¹²

Early treatment with leuporelin (either monotherapy or in CAB) has a demonstrated antitumor effect, suggesting that this is a reasonable treatment option for participants with localized or locally advanced or PCa where RP is not planned.¹⁰

AEs from leuporelin included hot flushes,^{8,13} nasopharyngitis,³ febrile neutropenia,¹⁶ and abnormal hepatic function.¹ Other AEs caused by ADT such as obesity,¹⁷ osteoporosis,¹⁸ sarcopenia,¹⁹ cognitive decline,²⁰ cardiovascular events,²¹ and depression²⁰ were examined in these studies. Many studies with high level of evidence have reported increased rates of cardiovascular side effects during ADT.^{21–24} Conversely, there are also a number of studies that dispute these findings.^{25–29}

Global health status and QOL were improved from baseline in participants treated with leuporelin.^{2, 13, 14} In participants who received intermittent androgen suppression, QOL was improved in off-treatment periods when compared with on-treatment periods.¹⁴ When leuporelin was administered in combination with steroidal antiandrogens such as CMA, participants had fewer and less distressing hot flushes than when treated with CAB and bicalutamide.¹³

2.1. Limitations

The few available publications were further limited by using an English language-only search strategy. Furthermore, many articles published on PCa have been Japanese, so its applicability to the wider Asian population is uncertain. Currently, there are no studies comparing the efficacy and safety of leuporelin between Asian and Western men. The differences in their response to leuporelin could only be inferred. A study on Korean men reported breakthrough rates (>50 ng/dL) of 5.0% when leuporelin was administered either as a monotherapy or in CAB.³⁰ Conversely, a study on Western men reported 24.7% of patients experienced a breakthrough rate (>50 ng/dL) when treated with leutinizing hormone–releasing hormone agonists with or without an antiandrogen.³¹ Unfortunately, the comparison of leutinizing hormone–releasing hormone agonist efficacy between these two populations is confounded by variables such as the method of testosterone measurement and study design. Hence, future studies are required to distinguish the efficacy and safety of leuporelin between these two groups.

3. Conclusions

Clinical trials of leuporelin conducted in Asia show that it is effective in decreasing serum testosterone and PSA levels to castration levels while improving QOL outcomes. Leuporelin may also be appropriate and effective in patients with PCa, with

radiation being another feasible option. Leuporelin AEs included hot flushes and mild hepatic dysfunction.

Conflict of interest

Dr. Horie reports receiving grants and personal fees from Takeda Pharmaceutical Company Ltd, Sanofi, and Astellas Pharma and personal fees from AstraZeneca and Janssen Pharmaceutica, outside the submitted work. Dr. Chiong reports receiving nonfinancial support from Takeda Pharmaceutical Company Ltd, during the conduct of the study. Dr. Chung reports receiving nonfinancial support from Takeda Pharmaceutical Company Ltd., during the conduct of the study; grants and personal fees from Janssen Pharmaceutica (USA & Korea), Bayer (Germany), Pfizer (USA), AstraZeneca (UK), Roche (Switzerland), and Myovant Sciences GmbH (Australia) and personal fees from Astellas Pharma (Korea), Ipsen (Korea), JW Pharmaceutical (Korea), Takeda Pharmaceutical Company Ltd (Korea), Handok (Korea), and Amgen (Korea), outside the submitted work.

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