SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 28: 319, 2024

Comparison of the efficacy and safety profiles of generic and branded leuprorelin acetate microspheres in patients with prostate cancer

ZHIEN ZHOU, YI ZHOU, WEIGANG YAN, TIANRUI FENG and ZHEN LIANG

Department of Urology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, P.R. China

Received November 6, 2023; Accepted April 5, 2024

DOI: 10.3892/ol.2024.14452

Abstract. Leuprorelin acetate microspheres, a common gonadotropin-releasing hormone agonist, have certain clinical benefits for prostate cancer (PCa). The present study aimed to compare the efficacy and safety of generic and branded leuprorelin acetate microspheres in patients with PCa. The present retrospective, observational study included 116 patients with PCa who received generic (Boennuokang®; Beijing Biote Pharmaceutical Co., Ltd.) or branded (Enantone®; Takeda Pharmaceutical Company, Ltd.) leuprorelin acetate microspheres via injection (commonly 3.75 mg once every 4 weeks), defined as the test (n=64) and reference (n=52) groups, respectively. The present study showed that testosterone levels at month (M) 3 (P<0.001), M6 (P=0.012) and M12 (P<0.001) were decreased in the test group compared with the reference group. However, prostate-specific antigen (PSA) levels at baseline, M1, M3, M6 and M12 were not significantly different between the test and reference groups (all P>0.05). The median (interquartile range) testosterone and PSA levels at M12 were 15.50 ng/dl (10.00-31.25 ng/dl) and 0.01 ng/ml (0.01-0.10 ng/ml), respectively, in the test group and 28.00 ng/dl (22.00-37.00 ng/dl) and 0.02 ng/ml (0.01-0.16 ng/ml), respectively, in the reference group. No significant differences were observed in the M1-baseline, M3-baseline, M6-baseline and M12-baseline changes of testosterone or PSA levels between the two groups (all P>0.050). Additionally, the incidence of all adverse events was not significantly different between the two groups (all P>0.050). Overall, Boennuokang® leuprorelin acetate microspheres exhibited a similar efficacy for suppression of testosterone and PSA levels with a comparable safety profile compared with Enantone® leuprorelin acetate microspheres in patients with PCa.

Correspondence to: Dr Yi Zhou, Department of Urology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, 1 Shuaifuyuan, Dongcheng, Beijing 100730, P.R. China
E-mail: zhouyi_pumch@163.com

Key words: prostate cancer, Boennuokang®, Enantone®, treatment efficacy, safety profile

Introduction

Prostate cancer (PCa), mainly caused by genetic mutations in basal or luminal prostate epithelial cells, accounts for ~7% of newly diagnosed types of cancer in male patients globally (1,2). In China, the disease burden of PCa is heavy and its age-standardized incidence in male patients has shown an average annual percentage increment of 2.6% from 2008 to 2012 (3,4). Since PCa is a highly androgen-dependent disease, androgen deprivation therapy (ADT), with the goal of reducing circulating androgen levels, is widely applied in PCa management (5). For patients with PCa with lymph node metastasis after extended pelvic lymph node dissection, ADT is recommended as an early adjuvant therapy following radical prostatectomy (6). Furthermore, ADT is the foundational treatment for patients with high-risk stage III and IV PCa (7,8), which may be more prevalently applied in China since the proportion of metastatic PCa is higher in China (25-32%) compared with the United States (19%) and the United Kingdom (18%) (9).

ADT comprises bilateral orchiectomy as well as gonadotropin-releasing hormone (GnRH) agonists, such as leuprorelin, goserelin, histrelin and triptorelin, and antagonists, such as degarelix (10,11). Bilateral orchiectomy has been gradually replaced due to its irreversibility and side effects of psychological trauma (8). However, GnRH agonists, which have become increasingly administered in clinical practice since their development, function to suppress the secretion of testosterone by regulating luteinizing hormone and follicle-stimulating hormone in the hypothalamic-pituitary-gonadal axis (12,13).

Leuprorelin is a long-acting GnRH agonist that primarily acts on the anterior pituitary, the continuous use of which causes the desensitization of the pituitary and further suppresses circulating gonadotrophins (14). Leuprorelin acetate microspheres were initially developed by Takeda Pharmaceutical Company, Ltd., and have been approved for PCa treatment in China since 2003, with the brand name Enantone® (15). A number of studies have reported the efficacy and safety of Enantone® leuprorelin acetate microspheres in

the treatment of PCa (16-20). For example, a previous study demonstrated that after Enantone® leuprorelin acetate microsphere monotherapy, serum testosterone levels decreased over time in patients with PCa, whose mean level at baseline, 3, 6 and 9 months was 460.2, 9.6, 8.7 and 6.8 ng/dl, respectively (16). Furthermore, another study found that Enantone® leuprorelin acetate microsphere ADT treatment resulted in a favorable pathologic response in 21% of patients with high-risk localized PCa (17). Notably, Boennuokang® leuprorelin acetate microspheres, as the first generic and domestic product developed by Beijing Biote Pharmaceutical Co., Ltd., have provided another treatment option for patients with PCa. At present, some studies have reported the favorable efficacy of Boennuokang® leuprorelin acetate microspheres for controlling prostate-specific antigen (PSA) levels, improving voluntary urination and elevating the quality of life in patients with PCa (21-23). Nevertheless, although Boennuokang® and Enantone® leuprorelin acetate microspheres are both commonly used for PCa treatment in China, to the best of our knowledge, their efficacy and safety have not been compared. Therefore, the present study aimed to compare the efficacy and safety profile of Boennuokang® and Enantone® leuprorelin acetate microspheres in patients with PCa.

Materials and methods

Patients. The present retrospective, observational, single-center study included 116 patients with PCa who received leuprorelin acetate microspheres via injection (Boennuokang® or Enantone®) between January 2017 and April 2022. The inclusion criteria were: i) Diagnosed with PCa via pathological examination; ii) treated with Boennuokang® or Enantone®; iii) aged >18 years old; and iv) with a complete medical history. The exclusion criteria were: i) History of surgical castration or pharmacologic endocrine therapy; ii) diagnosed with hematological malignancies or other types of cancer; iii) suffers from dysfunction of organs, such as heart, liver or kidneys; and iv) is missing information on key data, such as testosterone or PSA levels. The present study obtained approval from the Ethics Committee of Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences (approval no. I-23PJ473; Beijing, China), and the committee waived the requirement for informed consent.

Treatment. At Peking Union Medical College Hospital (Beijing, China), generic leuprorelin acetate microspheres (Boennuokang®; Beijing Biote Pharmaceutical Co., Ltd.; 3.75 mg depot formulation) and branded leuprorelin acetate microspheres (Enantone®; Takeda Pharmaceutical Company, Ltd.; 3.75 mg depot formulation) were administered via injection and were used to treat PCa. The common dosage and usage for both Boennuokang® and Enantone® was 3.75 mg once every 4 weeks according to the package insert. Patients who received Boennuokang® were considered to be the test group, while those who received Enantone® were considered to be the reference group. Patients received appropriate therapy (laparoscopic radical prostatectomy, endocrine therapy or radiotherapy) based on their disease status according to the National Comprehensive Cancer Network (NCCN) guideline (24) and other medications were administered as required.

Data collection. Clinical characteristics of patients with PCa were screened from their medical records, which involved demographics and disease information. Data on testosterone and PSA levels at baseline, 1 (M1), 3 (M3), 6 (M6) and 12 months (M12) after treatment were collected to evaluate efficacy, and data on adverse events from baseline to M12 were collected for safety evaluation. In addition, follow-up data including castration-resistant PCa-free survival (CRPC-FS) and overall survival (OS) were retrieved. CRPC-FS was defined as the time in months between the date of diagnosis and the date of occurrence of CRPC or last follow-up. OS was defined as the time in months between the date of diagnosis and the date of any-cause death or last follow-up. The last follow-up date was 7th March, 2024, and the follow-up duration ranged from 1 to 86 months.

Statistical analysis. SPSS v.26.0 (IBM Corp.) was used for data analysis and GraphPad Prism 7.01 (Dotmatics) was used for figure construction. The Kolmogorov-Smirnov test was used to test the normality of continuous variables. Continuous variables that did not follow a normal distribution are presented as the median [interquartile range (IQR)], while those following a normal distribution are presented as the mean ± standard deviation. Categorical variables are presented as the number (percentage). A Wilcoxon rank-sum test, unpaired Student's t-test, χ^2 test or Fisher's exact test was used for comparisons between groups. Specifically, the Wilcoxon rank-sum test was used to compare non-normally distributed variables between groups. Student's t-test was used to compare normally distributed variables between groups. The χ^2 test or Fisher's exact test was used to compare categorical variables between groups. Kaplan-Meier curves were generated to show CRPC-FS or OS rates, and the log-rank test was used to compare the rates between groups. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient selection. A total of 494 patients with PCa receiving Boennuokang® or Enantone® leuprorelin acetate microspheres for treatment were assessed. Among them, 271 patients who did not use Boennuokang® or Enantone® leuprorelin acetate microspheres as the initial ADT drugs, 46 patients who lacked data on testosterone levels at baseline, 29 patients who changed ADT drugs during the first year of observation and 32 patients whose testosterone level detection time interval did not meet the requirements were excluded. Finally, 116 patients with PCa were included in the analysis, and the process of patient selection with inclusion and exclusion data is shown in Fig. 1.

Clinical characteristics of the test and reference groups. The mean age of the test and reference groups was 74.2±8.8 years (ranging from 49 to 90 years) and 74.1±8.1 years (ranging from 57 to 90 years), respectively. The mean Gleason score was 7.6±1.2 and 7.7±0.9 in the test and reference group, respectively. With respect to the tumor grade, 8 (12.5%), 10 (15.6%), 10 (15.6%), 7 (10.9%) and 13 (20.3%) patients in the test group were evaluated as having International Society of Urological Pathology (ISUP) (25) grade 1, 2, 3, 4 and 5, respectively, and the ISUP grade for the remaining 16 (25.0%) patients was

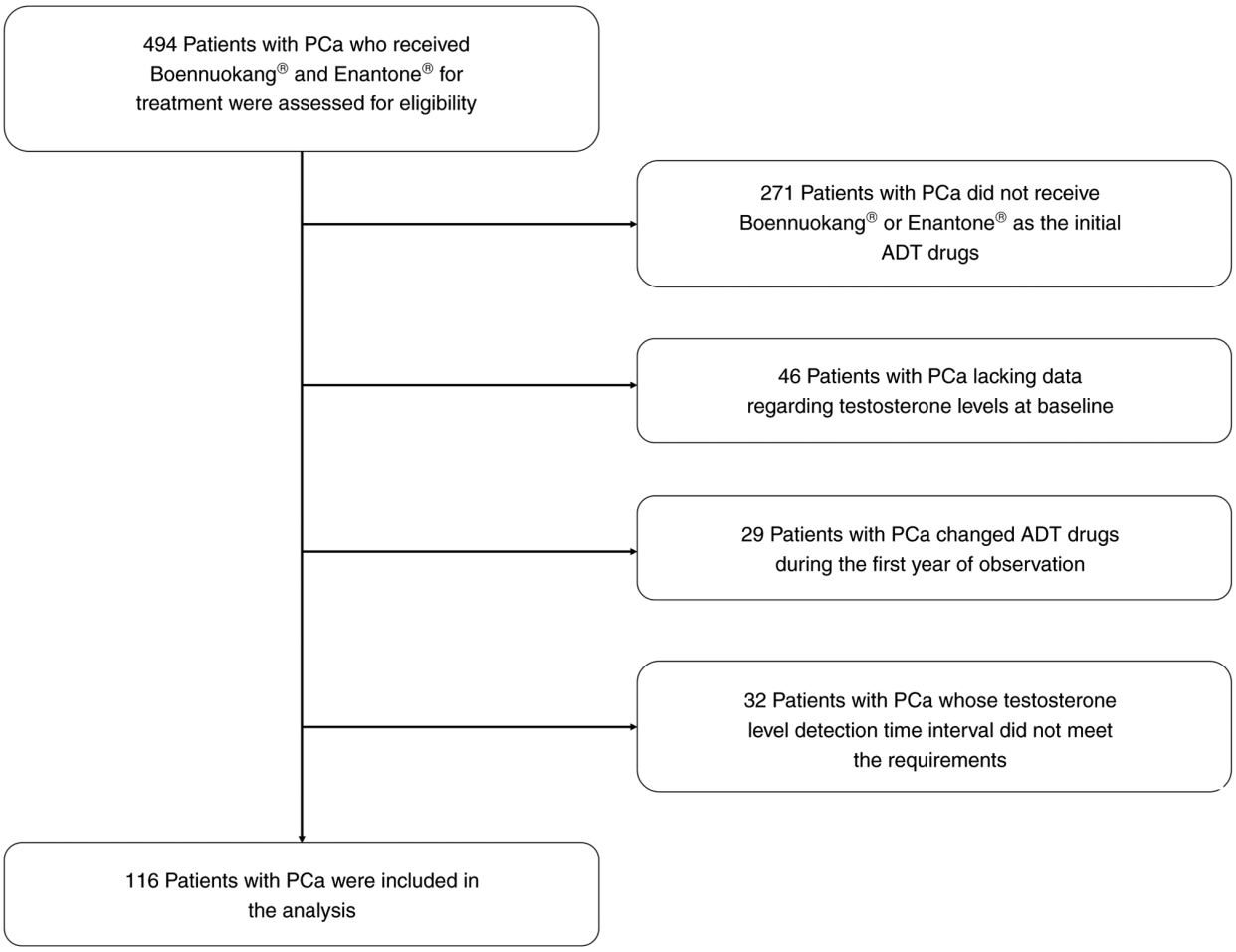

Figure 1. Flow chart of patient selection. PCa, prostate cancer; ADT, androgen deprivation therapy.

unavailable. In the reference group, there were 2 (3.8%), 6 (11.5%), 9 (17.3%), 11 (21.2%) and 8 (15.4%) patients that were identified as having ISUP grade 1, 2, 3, 4 and 5, respectively. The ISUP grade was unknown in the remaining 16 (30.8%) patients. The percentage of patients with ISUP grade 1 and 2 was not different between the test group and the reference group (28.1 vs. 15.3%; P=0.102). Notably, clinical characteristics, including age, Gleason score, ISUP grade, tumor node metastasis stage, treatment regimens, baseline testosterone levels and baseline PSA levels, did not vary between the test group and the reference group (all P>0.05; Table I).

Comparison of testosterone and PSA levels between the test and reference groups. Testosterone levels at M3 (P<0.001), M6 (P=0.012) and M12 (P<0.001) were decreased in the test group compared with the reference group, but testosterone levels at baseline (P=0.635) and M1 (P=0.076) were not significantly different. The detailed testosterone levels at different timepoints in the two groups are listed in Table II.

PSA levels at baseline (P=0.145), M1 (P=0.489), M3 (P=0.712), M6 (P=0.590) and M12 (P=0.444) did not vary between the test and reference groups. The detailed PSA levels at different timepoints in the two groups are shown in Table II.

Comparison of changes in testosterone levels between the test and reference groups. Following treatment, testosterone levels decreased in both groups and no difference was seen in M1-baseline (P=0.441), M3-baseline (P=0.463), M6-baseline (P=0.598) or M12-baseline (P=0.520) changes in testosterone levels between the test and reference groups. Specifically, the median (IQR) M1-baseline, M3-baseline, M6-baseline and M12-baseline changes in testosterone levels were -292.00 ng/dl (-387.50 to -239.50 ng/dl), -303.00 ng/dl (-391.00 to -245.00 ng/dl), -306.00 ng/dl (-391.00 to -247.00 ng/dl) and -305.50 ng/dl (-388.00 to -241.75 ng/dl), respectively, in the test group. The median (IQR) M1-baseline, M3-baseline, M6-baseline and M12-baseline changes in testosterone levels were -290.00 ng/dl (-389.00 to -215.00 ng/dl), -288.00 ng/dl (-385.00 to -219.50 ng/dl), -296.00 ng/dl (-388.00 to -227.00 ng/dl) and -293.00 ng/dl (-391.00 to -225.00 ng/dl), respectively, in the reference group (Table III).

Comparison of changes in PSA levels between the test and reference groups. The test and reference groups both exhibited decreased PSA levels after treatment, but the M1-baseline (P=0.286), M3-baseline (P=0.144), M6-baseline (P=0.158) and M12-baseline (P=0.270) PSA changes were not significantly different between the test and reference groups. Specifically, the median (IQR) M1-baseline, M3-baseline, M6-baseline and M12-baseline changes in PSA levels in the test group were -10.00 ng/ml (-28.53 to -5.13 ng/ml), -11.60 ng/ml (-32.10 to -7.90 ng/ml), -11.78 ng/ml (-36.70 to -8.00 ng/ml) and

Table I. Clinical characteristics of patients with prostate cancer.

Characteristics	Test group (n=64)	Reference group (n=52)	P-value
Age (years), mean ± SD	74.2±8.8	74.1±8.1	0.970[a]
Gleason score, mean ± SD	7.6±1.2	7.7±0.9	0.638[a]
ISUP grade, n (%)			0.369[b]
1	8 (12.5)	2 (3.8)	
2	10 (15.6)	6 (11.5)	
3	10 (15.6)	9 (17.3)	
4	7 (10.9)	11 (21.2)	
5	13 (20.3)	8 (15.4)	
NA	16 (25.0)	16 (30.8)	
ISUP grade 1&2, n (%)	18 (28.1)	8 (15.3)	0.102[c]
TNM stage, n (%)			0.100[c]
II	21 (32.8)	7 (13.5)	
III	16 (25.0)	18 (34.6)	
IV	11 (17.2)	13 (25.0)	
NA	16 (25.0)	14 (26.9)	
Treatment regimens, n (%)			
Endocrine therapy only	34 (53.1)	21 (40.4)	0.172[c]
Radiotherapy combined with endocrine therapy	20 (31.3)	23 (44.2)	0.150[c]
Laparoscopic radical prostatectomy combined with endocrine therapy	10 (15.6)	8 (15.4)	0.972[c]

P-value calculated using a [a]Student's t-test, [b]Fisher's exact test, and [c]χ^2 test. ISUP, International Society of Urological Pathology; IQR, interquartile range; PSA, prostate-specific antigen; NA, relevant data were missing or unavailable.

-11.89 ng/ml (-37.16 to -8.09 ng/ml), respectively. Meanwhile, in the reference group, the median (IQR) PSA changes at these time points were -14.13 ng/ml (-34.53 to -9.04 ng/ml), -16.86 ng/ml (-42.90 to -10.10 ng/ml), -16.89 ng/ml (-43.62 to -10.11 ng/ml) and -17.14 ng/ml (-43.79 to -10.07 ng/ml), respectively (Table IV).

Comparison of long-term outcomes between the test and reference groups. CRPC-FS did not differ between the test group and the reference group (P=0.550). In detail, the 1-, 3- and 5-year CRPC-FS rates in the test group were 90.2, 78.6 and 78.6%, and these were 90.7, 76.2 and 64.3% in the reference group (Fig. S1A). OS did not vary between the test and reference groups (P=0.437). Specifically, the 1-, 3- and 5-year OS rates in the test group were 98.4, 95.0 and 95.0%, and these were 97.1, 89.9 and 81.7% in the reference group (Fig. S1B).

Comparison of adverse events between the test and reference groups. Generally, the adverse events were controllable in both the test and reference groups. The most common adverse events in the test group were fatigue (20.3%), weight gain (17.2%) and sweating (15.6%). Similarly, the most common adverse events in the reference group were sweating (21.2%), weight gain (19.2%) and fatigue (17.3%). Notably, no significant difference was observed in the frequency of each adverse event, including fatigue (P=0.681), weight gain (P=0.776), sweating (P=0.442), elevated blood lipids (P=0.478), lower urinary tract symptoms (P=0.690), elevated blood glucose levels (P=0.699), elevated transaminase levels (P>0.999), tachycardia (P>0.999) and bloody stool (P=0.448), between the test and reference groups. Furthermore, 1 patient in the reference group experienced bloody stool, which was induced by radiation enteritis (Table V).

Subgroup analysis. Further subgroup analysis was conducted in patients receiving different treatment regimens, which showed that, in patients with PCa treated with endocrine therapy only and patients who received laparoscopic radical prostatectomy combined with endocrine therapy, PSA levels at baseline, M1, M3, M6 and M12 were not significantly different between the test and reference groups (all P>0.050). In patients receiving radiotherapy combined with endocrine therapy, PSA levels at baseline (P<0.001) and M1 (P=0.004) were decreased in the test group compared with the reference group, but there was no difference in PSA levels between the two groups at M3, M6 and M12 (Table VI).

Discussion

At present, there are few clinical reports describing Boennuokang® leuprorelin acetate microspheres in the treatment of PCa, and their use has been reported in only three previous studies (21-23). As reported in one randomized, controlled study, patients with PCa treated with Boennuokang® leuprorelin acetate microspheres plus bicalutamide and radiotherapy had decreased PSA levels compared with those treated with radiotherapy alone, with a mean PSA level of

Table II. Testosterone and PSA levels of patients with prostate cancer at different time points.

Item	Test group	Reference group	P-value
Testosterone levels (ng/dl)			
Baseline			
Number of assessed patients	64	52	
Median (IQR)	324.00 (264.50-417.50)	319.00 (256.50-421.00)	0.635[a]
M1			
Number of assessed patients	61	51	
Median (IQR)	32.00 (17.00-45.00)	37.00 (26.00-47.00)	0.076[a]
M3			
Number of assessed patients	63	49	
Median (IQR)	22.00 (10.00-29.00)	31.00 (23.50-37.00)	<0.001[a]
M6			
Number of assessed patients	63	51	
Median (IQR)	21.00 (10.00-33.00)	31.00 (19.00-37.00)	0.012[a]
M12			
Number of assessed patients	62	51	
Median (IQR)	15.50 (10.00-31.25)	28.00 (22.00-37.00)	<0.001[a]
PSA levels (ng/ml)			
Baseline			
Number of assessed patients	64	52	
Median (IQR)	11.70 (8.08-35.54)	17.43 (10.39-42.77)	0.145[a]
M1			
Number of assessed patients	57	48	
Median (IQR)	2.35 (0.86-4.34)	2.62 (0.58-8.35)	0.489[a]
M3			
Number of assessed patients	61	47	
Median (IQR)	0.17 (0.06-0.44)	0.24 (0.04-0.96)	0.712[a]
M6			
Number of assessed patients	60	47	
Median (IQR)	0.03 (0.01-0.14)	0.04 (0.01-0.38)	0.590[a]
M12			
Number of assessed patients	59	47	
Median (IQR)	0.01 (0.01-0.10)	0.02 (0.01-0.16)	0.444[a]

[a]P-value calculated using the Wilcoxon rank sum test. PSA, prostate-specific antigen; IQR, interquartile range; M1, 1st month after treatment; M3, 3rd month after treatment; M6, 6th month after treatment; M12, 12th month after treatment.

15.69±3.57 and 22.38±5.24 ng/ml, respectively, at M2 after treatment (21). Similarly, another study noted that the combination of Boennuokang® leuprorelin acetate microspheres and intensity-modulated radiotherapy resulted in an improved PSA suppression effect and elevated 1/2-year survival rates compared with intensity-modulated radiotherapy alone in patients with PCa (22). Furthermore, a previous study examined administration of Boennuokang® leuprorelin acetate microspheres in patients with PCa complicated with urinary retention. After 16 weeks of treatment, the maximum urinary flow rate was improved and the prostate volume was reduced in these patients (23). The aforementioned studies indicate the positive clinical efficacy of Boennuokang® leuprorelin acetate microspheres in PCa treatment (21-23). In the current study, both testosterone and PSA levels were reduced after Boennuokang® leuprorelin acetate microsphere treatment in patients with PCa, and the median (IQR) M12-baseline testosterone and PSA changes reached -305.50 ng/dl (-388.00 to -241.75 ng/dl) and -11.89 ng/ml (-37.16 to -8.09 ng/ml), respectively. This positive performance could be explained by leuprorelin acetate microspheres possessing a resistance to proteolytic enzymes and a high affinity to the GnRH receptor, and therefore leuprorelin acetate microspheres effectively inhibits the pituitary-gonadal system (15).

Concerning the application of Enantone® leuprorelin acetate microspheres in patients with PCa, one case report described a patient with PCa with lung metastases receiving Enantone® leuprorelin acetate microsphere injection and oral bicalutamide as the first-line therapy, who achieved a stable disease state during the 3-year follow-up (26). Furthermore, another study reported that the administration of Enantone® leuprorelin acetate microspheres plus flutamide once a month

Table III. Changes in testosterone levels of patients with prostate cancer.

Item	Test group	Reference group	P-value
M1-baseline			
Number of assessed patients	61	51	
Median (IQR), ng/dl	-292.00 (-387.50 to -239.50)	-290.00 (-389.00 to -215.00)	0.441[a]
M3-baseline			
Number of assessed patients	63	49	
Median (IQR), ng/dl	-303.00 (-391.00 to -245.00)	-288.00 (-385.00 to -219.50)	0.463[a]
M6-baseline			
Number of assessed patients	63	51	
Median (IQR), ng/dl	-306.00 (-391.00 to -247.00)	-296.00 (-388.00 to -227.00)	0.598[a]
M12-baseline			
Number of assessed patients	62	51	
Median (IQR), ng/dl	-305.50 (-388.00 to -241.75)	-293.00 (-391.00 to -225.00)	0.520[a]

[a]P-value calculated using the Wilcoxon rank sum test. M1, 1st month after treatment; IQR, interquartile range; M3, 3rd month after treatment; M6, 6th month after treatment; M12, 12th month after treatment.

Table IV. Changes in prostate-specific antigen levels of patients with prostate cancer.

Item	Test group	Reference group	P-value
M1-baseline			
Number of assessed patients	57	48	
Median (IQR), ng/ml	-10.00 (-28.53 to -5.13)	-14.13 (-34.53 to -9.04)	0.286[a]
M3-baseline			
Number of assessed patients	61	47	
Median (IQR), ng/ml	-11.60 (-32.10 to -7.90)	-16.86 (-42.90 to -10.10)	0.144[a]
M6-baseline			
Number of assessed patients	60	47	
Median (IQR), ng/ml	-11.78 (-36.70 to -8.00)	-16.89 (-43.62 to -10.11)	0.158[a]
M12-baseline			
Number of assessed patients	59	47	
Median (IQR), ng/ml	-11.89 (-37.16 to -8.09)	-17.14 (-43.79 to -10.07)	0.270[a]

[a]P-value calculated using the Wilcoxon rank sum test. M1, 1st month after treatment; IQR, interquartile range; M3, 3rd month after treatment; M6, 6th month after treatment; M12, 12th month after treatment.

resulted in a decreased testosterone concentration and PSA levels in 16 patients with PCa (27). Similarly, the present study revealed that treatment with Enantone® leuprorelin acetate microspheres resulted in decreased testosterone and PSA levels in patients with PCa. Specifically, the median (IQR) M12-baseline testosterone and PSA changes were -293.00 ng/dl (-391.00 to -225.00 ng/dl) and -17.14 ng/ml (-43.79 to -10.07 ng/ml), respectively. This could also be explained by the drug acting as a GnRH agonist (with a strong inhibiting role against gonadotropin secretion) as aforementioned (14).

To the best of our knowledge, the present study was the first to compare the treatment efficacy of Boennuokang® and Enantone® leuprorelin acetate microspheres in patients with PCa. It was observed that M1-baseline, M3-baseline, M6-baseline or M12-baseline testosterone and PSA changes were not varied between the two groups. This may have been due to Boennuokang® and Enantone® leuprorelin acetate microspheres sharing similar components, including the active substance leuprorelin acetate and polymers of lactic acids, resulting in their similar treatment efficacy (15). Furthermore, it was noted that testosterone levels at M3, M6 and M12 were decreased in patients with PCa who received Boennuokang® leuprorelin acetate microspheres compared with those who received Enantone® leuprorelin acetate microspheres. These findings may be affected by the more advanced microsphere preparation process, as Boennuokang® was launched later, or by the relatively small sample size. Therefore, further studies with a larger sample size are required for validation.

Table V. Adverse events.

Events	Test group, n (%) (n=64)	Reference group, n (%) (n=52)	P-value
Fatigue	13 (20.3)	9 (17.3)	0.681[a]
Weight gain	11 (17.2)	10 (19.2)	0.776[a]
Sweating	10 (15.6)	11 (21.2)	0.442[a]
Elevated blood lipid	7 (10.9)	8 (15.4)	0.478[a]
LUTS	4 (6.3)	2 (3.8)	0.690[b]
Elevated blood glucose	3 (4.7)	4 (7.7)	0.699[b]
Elevated transaminase	2 (3.1)	1 (1.9)	>0.999[b]
Tachycardia	1 (1.6)	1 (1.9)	>0.999[b]
Bloody stool	0 (0.0)	1 (1.9)	0.448[b]

P-value calculated using the [a]χ^2 test and [b]Fisher's exact test. LUTS, lower urinary tract symptoms.

Table VI. Subgroup analysis of prostate-specific antigen levels.

Subgroup	Test group	Reference group	P-value
Endocrine therapy only			
Number of assessed patients	34	21	
Baseline, median (IQR), ng/ml	24.93 (8.52-80.05)	14.85 (5.60-171.00)	0.872[a]
M1, median (IQR), ng/ml	2.86 (0.69-6.43)	1.45 (0.35-13.85)	0.420[a]
M3, median (IQR), ng/ml	0.22 (0.09-1.14)	0.11 (0.03-0.96)	0.409[a]
M6, median (IQR), ng/ml	0.06 (0.02-0.53)	0.05 (0.01-0.80)	0.812[a]
M12, median (IQR), ng/ml	0.04 (0.01-0.23)	0.10 (0.01-1.18)	0.784[a]
Radiotherapy combined with endocrine therapy			
Number of assessed patients	20	23	
Baseline, median (IQR), ng/ml	9.27 (6.39-15.83)	19.23 (14.10-32.60)	<0.001[a]
M1, median (IQR), ng/ml	2.08 (1.05-3.17)	3.60 (2.50-8.40)	0.004[a]
M3, median (IQR), ng/ml	0.18 (0.03-0.59)	0.43 (0.08-1.43)	0.054[a]
M6, median (IQR), ng/ml	0.01 (0.01-0.09)	0.04 (0.01-0.38)	0.074[a]
M12, median (IQR), ng/ml	0.01 (0.01-0.06)	0.02 (0.01-0.12)	0.174[a]
Laparoscopic radical prostatectomy combined with endocrine therapy			
Number of assessed patients	10	8	
Baseline, median (IQR), ng/ml	10.10 (8.10-30.08)	7.83 (3.32-50.90)	0.570[a]
M1, median (IQR), ng/ml	2.49 (1.05-3.29)	1.09 (0.15-3.40)	0.570[a]
M3, median (IQR), ng/ml	0.06 (0.01-0.14)	0.01 (0.01-0.04)	0.100[a]
M6, median (IQR), ng/ml	0.01 (0.00-0.02)	0.01 (0.01-0.01)	0.785[a]
M12, median (IQR), ng/ml	0.01 (0.00-0.01)	0.01 (0.01-0.80)	0.525[a]

[a]P-value calculated using the Wilcoxon rank-sum test. M1, 1st month after treatment; IQR, interquartile range; M3, 3rd month after treatment; M6, 6th month after treatment; M12, 12th month after treatment.

The reliable safety profile of leuprorelin acetate microspheres has been previously reported (28-31); fatigue, weight gain, hot flushes and sweating are the common adverse events recorded in patients with PCa who receive leuprorelin acetate microsphere treatment (28-31). The present study also showed good tolerance of Boennuokang® and Enantone® leuprorelin acetate microspheres in patients with PCa, and the most common adverse events, including fatigue, weight gain and sweating, were consistent with previous studies (28,29), while hot flushes were not observed in this study, which may be explained as follows: It was a retrospective observational study and the adverse events may be underestimated. Furthermore, the incidence of adverse events was not statistically different between the Boennuokang® and Enantone® leuprorelin acetate microsphere groups, indicating that they had a similar safety profile in patients with PCa.

The present study has some limitations. First, it was a retrospective, observational, single-center study, and the comparable treatment efficacy of Boennuokang® and Enantone® leuprorelin acetate microspheres should be validated in further multicenter, randomized, controlled studies. Second, the adverse events were only collected within a short-term follow-up period, and the long-term side effects of both Boennuokang® and Enantone® leuprorelin acetate microspheres were hard to monitor. Given that ADT can be continuously used for maintenance in patients with PCa (12), the long-term side effects should be investigated in further studies. Third, given that the dosage of leuprorelin acetate microspheres was fixed, data on drug concentrations and metabolism were not collected in the present study, and these require further investigation. Fourth, the percentage of patients with ISUP grade 1 and 2 in the test group was numerically higher than that in the reference group (without statistical significance), which could potentially lead to relatively better clinical outcomes in the test group compared to the reference group.

In conclusion, Boennuokang® leuprorelin acetate microspheres may have a comparable efficacy for testosterone and PSA suppression with similar tolerance compared with Enantone® leuprorelin acetate microspheres in patients with PCa. However, the findings need further validation through a randomized controlled study with a larger sample size and longer follow-up duration.

Acknowledgements

Not applicable.

Funding

The present study was supported by National High Level Hospital Clinical Research Funding (grant nos. 2022-PUMCH-B-009 and 2022-PUMCH-A-063).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ZZ, YZ, WY, TF and ZL contributed to the study conception and design. Material preparation, and data collection and analysis were performed by ZZ, YZ and WY. ZZ, YZ, WY, TF and ZL contributed to the first draft of the manuscript and commented on previous versions of the manuscript. TF and ZL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study obtained approval from the Ethics Committee of Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences (approval no. I-23PJ473; Beijing, China), and the committee waived the requirement for informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Rebello RJ, Oing C, Knudsen KE, Loeb S, Johnson DC, Reiter RE, Gillessen S, Van der Kwast T and Bristow RG: Prostate cancer. Nat Rev Dis Primers 7: 9, 2021.
2. Sekhoacha M, Riet K, Motloung P, Gumenku L, Adegoke A and Mashele S: Prostate cancer review: Genetics, diagnosis, treatment options, and alternative approaches. Molecules 27: 5730, 2022.
3. Sun D, Li H, Cao M, He S, Lei L, Peng J and Chen W: Cancer burden in China: Trends, risk factors and prevention. Cancer Biol Med 17: 879-895, 2020.
4. Qiu H, Cao S and Xu R: Cancer incidence, mortality, and burden in China: A time-trend analysis and comparison with the United States and United Kingdom based on the global epidemiological data released in 2020. Cancer Commun (Lond) 41: 1037-1048, 2021.
5. Williams IS, McVey A, Perera S, O'Brien JS, Kostos L, Chen K, Siva S, Azad AA, Murphy DG, Kasivisvanathan V, *et al*: Modern paradigms for prostate cancer detection and management. Med J Aust 217: 424-433, 2022.
6. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, Fanti S, Fossati N, Gandaglia G, Gillessen S, *et al*: EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer-2020 update. Part 1: Screening, diagnosis, and local treatment with curative intent. Eur Urol 79: 243-262, 2021.
7. Desai K, McManus JM and Sharifi N: Hormonal therapy for prostate cancer. Endocr Rev 42: 354-373, 2021.
8. Crawford ED, Heidenreich A, Lawrentschuk N, Tombal B, Pompeo ACL, Mendoza-Valdes A, Miller K, Debruyne FMJ and Klotz L: Androgen-targeted therapy in men with prostate cancer: Evolving practice and future considerations. Prostate Cancer Prostatic Dis 22: 24-38, 2019.
9. Zhu Y, Mo M, Wei Y, Wu J, Pan J, Freedland SJ, Zheng Y and Ye D: Epidemiology and genomics of prostate cancer in Asian men. Nat Rev Urol 18: 282-301, 2021.
10. Iwamoto H, Izumi K, Makino T and Mizokami A: Androgen deprivation therapy in high-risk localized and locally advanced prostate cancer. Cancers (Basel) 14: 1803, 2022.
11. Yu EM and Aragon-Ching JB: Advances with androgen deprivation therapy for prostate cancer. Expert Opin Pharmacother 23: 1015-1033, 2022.
12. Merseburger AS, Hammerer P, Rozet F, Roumeguère T, Caffo O, da Silva FC and Alcaraz A: Androgen deprivation therapy in castrate-resistant prostate cancer: How important is GnRH agonist backbone therapy? World J Urol 33: 1079-1085, 2015.
13. Raja T, Sud R, Addla S, Sarkar KK, Sridhar PS, Talreja V, Jain M and Patil K: Gonadotropin-releasing hormone agonists in prostate cancer: A comparative review of efficacy and safety. Indian J Cancer 59: S142-S159, 2022.
14. Persad R: Leuprorelin: A leading role in advanced prostate cancer therapy. Hosp Med 64: 360-363, 2003.
15. Wilson AC, Meethal SV, Bowen RL and Atwood CS: Leuprolide acetate: A drug of diverse clinical applications. Expert Opin Investig Drugs 16: 1851-1863, 2007.
16. Shim M, Bang WJ, Oh CY, Lee YS and Cho JS: Effectiveness of three different luteinizing hormone-releasing hormone agonists in the chemical castration of patients with prostate cancer: Goserelin versus triptorelin versus leuprolide. Investig Clin Urol 60: 244-250, 2019.
17. McKay RR, Xie W, Ye H, Fennessy FM, Zhang Z, Lis R, Calagua C, Rathkopf D, Laudone VP, Bubley GJ, *et al*: Results of a randomized phase II trial of intense androgen deprivation therapy prior to radical prostatectomy in men with high-risk localized prostate cancer. J Urol 206: 80-87, 2021.
18. Mizokami A, Ueno S, Fukagai T, Ito K, Ehara H, Kinbara H, Origasa H, Usami M, Namiki M and Akaza H: Global update on defining and treating high-risk localized prostate cancer with leuprorelin: An Asian perspective. BJU Int 99 (Suppl 1): S6-S9; discussion 17-18, 2007.

19. Suzuki K, Namiki M, Fujimoto T, Takabayashi N, Kudou K and Akaza H: Efficacy and safety of leuprorelin acetate 6-month depot in prostate cancer patients: A phase III, randomized, open-label, parallel-group, comparative study in Japan. Jpn J Clin Oncol 45: 1168-1174, 2015.
20. Chung BH, Horie S and Chiong E: Clinical studies investigating the use of leuprorelin for prostate cancer in Asia. Prostate Int 8: 1-9, 2020.
21. Li WL, Shi QB, Han WH and Li CM: Influence on efficacy and immune function in patients with prostate cancer by using intensity-modulated radiotherapy combined with endocrine therapy. Pract J Cancer 34: 1275-1279, 2019 (In Chinese).
22. Su JQ, Xin JH, Zhao XR and Guan MG: The effect of intensity-modulated radiotherapy combined with endocrine therapy on prostate cancer. Guide Chin Med 5: 110-112, 2022 (In Chinese).
23. Ling KN, Yang JR, Li BJ, Li J, Ji ZQ and Liu JZ: A study on the clinical efficacy of medical castration in treatment of prostate cancer complicated with urinary retention. Chin J Clin Med 15: 340-344, 2022 (In Chinese).
24. Mohler JL, Armstrong AJ, Bahnson RR, D'Amico AV, Davis BJ, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, *et al*: Prostate cancer, version 1.2016. J Natl Compr Canc Netw 14: 19-30, 2016.
25. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR and Humphrey PA; Grading Committee: The 2014 international society of urological pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma: Definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 40: 244-252, 2016.
26. Wu LX, Lei L, Zhu YC, Du KQ, Li XF, Chen HF, Wang WX and Xu CW: A prostate cancer patient with isolated lung metastases: A case report. Transl Cancer Res 9: 2064-2068, 2020.
27. Zhang L, Tao D and Wang S: Clinical evaluation of enantone in the treatment of prostate cancer. Zhonghua Zhong Liu Za Zhi 19: 218-220, 1997 (In Chinese).
28. Padula GD, Zelefsky MJ, Venkatraman ES, Fuks Z, Lee HJ, Natale L and Leibel SA: Normalization of serum testosterone levels in patients treated with neoadjuvant hormonal therapy and three-dimensional conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 52: 439-443, 2002.
29. Marberger M, Kaisary AV, Shore ND, Karlin GS, Savulsky C, Mis R, Leuratti C and Germa JR: Effectiveness, pharmacokinetics, and safety of a new sustained-release leuprolide acetate 3.75-mg depot formulation for testosterone suppression in patients with prostate cancer: A phase III, open-label, international multicenter study. Clin Ther 32: 744-757, 2010.
30. George DJ, Saad F, Cookson MS, Saltzstein DR, Tutrone R, Bossi A, Brown B, Selby B, Lu S, Buckley D, *et al*: Impact of concomitant prostate cancer medications on efficacy and safety of relugolix versus leuprolide in men with advanced prostate cancer. Clin Genitourin Cancer 21: 383-392 e2, 2023.
31. LBA02-09 EMBARK: A Phase 3 randomized study of enzalutamide or placebo plus leuprolide acetate and enzalutamide monotherapy in high-risk biochemically recurrent prostate cancer. J Urol 210: 224-226, 2023.