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Serum testosterone suppression and potential for agonistic stimulation during chronic treatment with monthly depot formulation of domestic substitute of leuprorelin acetate microspheres for metastatic prostate cancer*

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Abstract ***Objective:*** We aimed to evaluate the efficiency of serum testosterone suppression as well as the potential for agonistic stimulation of serum testosterone during chronic treatment with monthly (3.75 mg) depot formulation of domestic substitute of leuprorelin acetate microspheres for patients with metastatic prostate cancer. ***Methods:*** A total of 23 patients with metastatic prostate cancer were enrolled in the prospective study and received 6 monthly intramuscular depot injections of domestic substitute of leuprorelin acetate microspheres. Their levels and patterns of serum testosterone suppression and the potential for agonistic stimulation of serum testosterone were monitored following injection monthly (3.75 mg) depot formulation of domestic substitute of leuprorelin acetate microspheres for 24 weeks. ***Results:*** Mean testosterone was 431.4 ng/dL, 119.3 ng/dL, 28.2 ng/dL by week 1, 2, 3 and decreased to less than 15.6 ng/dL by week 4 where it remained throughout the treatment period. Median time to suppression of serum testosterone was 20.7 days. No transient minor "escape" from suppression occurred in all patients which was defined as a single testosterone value greater than 50 ng/dL once suppression was achieved. Assessment of agonistic stimulation following the second depot injection revealed no pattern of stimulation. ***Conclusion:*** We concluded that monthly (3.75 mg) depot formulation of domestic substitute of leuprorelin acetate microspheres could provide persistent, stable suppression of serum testosterone throughout the dosing intervals, and that the initial depot injection of this formulation also could provide sufficient pituitary desensitization to prevent agnostic stimulation of serum testosterone during chronic treatment.

Key words prostatic neoplasms, metastatic; testosterone; leuprorelin; domestic substitute

Metastatic prostate cancer mainly depends on castration therapy to be controlled, or combined with other treatments such as chemotherapy and hopeful gene targeted therapy [1]. Agonistic analogues of gonadotropin releasing hormones (Gn-RH) are a type of widely used medicine for castration and indicated for the palliative treatment of metastatic prostate cancer and are also used as adjuvant therapy during and following radiotherapy and radical prostatectomy as well as neoadjuvant therapy before radical prostatectomy for locally advanced disease. These agents act by inducing downregulation of pituitary Gn-RH receptors and a consequent decrease in pituitary gonadotropin output. The ensuing reduction in testicular steroidogenesis and serum testosterone level to near castrate levels creates a hypoandrogenic environment resulting in slowing or cessation of androgen dependent tumor growth. Historically, greater than 70% of patients respond to hormonal manipulation until castrate-resistant disease eventually develops [2–4].

Leuprorelin acetate is an analogue of Gn-RH and has been shown to be an effective palliative agent for the treatment of advanced prostate cancer. It is available in a formulation administered as a daily subcutaneous in-

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jection, as well as several sustained release depot formulations administered intramuscularly on a monthly, 3-month or 4-month basis. Following initial administration of leuprorelin acetate, there is a transient increase in serum testosterone during the first week of treatment to a range considerably above the pretreatment level which is seen with all formulations of leuprorelin acetate. Then serum testosterone usually decreases to the nadir level (less than 50 ng/dL) within several weeks of the initial injection [5–8].

Monthly (3.75 mg) depot formulation of leuprorelin acetate microspheres for injection (Trade name: Bei Yi) is domestic substitute of leuprorelin acetate and made by Shanghai Livzon Pharmaceutical Co., Ltd., China. Until now, there is still no publication to evaluate its efficiency of serum testosterone suppression during chronic treatment for patients with metastatic prostate cancer.

We report results of a prospective study about the pattern of serum testosterone suppression as well as the potential for agonistic stimulation of serum testosterone following reinjection during treatment of metastatic prostate cancer with monthly (3.75 mg) depot formulation of domestic substitute of leuprorelin acetate microspheres.

Materials and methods

A total of 23 patients with metastatic prostatic adenocarcinoma, an intact hypothalamic-pituitary-gonadal axis and serum testosterone 150 ng/dL or greater were enrolled into the open prospective study involving 2 investigative hospitals in People's Republic of China between January 2013 and October 2013. The mean age was 77 years, with a range of 73–82 years. CT2NxM1 stage was found in 18 patients (78.3%) and CT3NxM1 stage in 24 patients (21.7%). Their total PSA values were 118.76–267 ng/mL. Patients must be the initial diagnosed for prostate cancer without receiving treatment with Gn-RH analogues or hormonal treatment within 6 months. Patients also had to have positive results on a bone scan for metastatic disease and biopsy readings.

Patients were to receive 6 monthly (29 to 31 days apart) intramuscular depot injections of the 3.75 mg formulation. Bicalutamide (50 mg per day) was taken orally simultaneously by all patients in their initial month of castration treatment. Serum testosterone levels were monitored for 24 weeks. Testosterone levels were obtained just before the initial depot injection (pretreatment or baseline) and at the end of weeks 2 to 8, as well as at the end of weeks 12, 16, 20 and 24. On dosing visits blood was drawn before the depot injection. Agonistic stimulation of testosterone was assessed at 4, 8 and 12 hours after the second depot injection.

Analyses of testosterone data were performed using all data from all 23 patients. Mean changes in serum testosterone from pretreating baseline to each treatment visit within 24 weeks were analyzed using a 2-way analysis of covariance with the baseline value as the covariate and effects for treatment. Mean changes from pre-injection baseline to 4, 8 and 12 h following the second injection were analyzed using this method, too.

Serum testosterone was considered to be suppressed if 2 consecutive (on separate days) values 50 ng/dL or less occurred. Onset of suppression was considered the day on which the first of these "suppressed" values occurred. An "escape" from suppression was defined as a single testosterone value greater than 50 ng/dl following the onset of suppression. Stimulation after reinjection was defined as the occurrence of testosterone level greater than 50 ng/dL at 4, 8 or 12 h following reinjection when the pre-injection testosterone value was 50 ng/dL or less.

Table 1 Mean testosterone values of 23 patients

Time	Mean testosterone values (ng/dL)
Baseline	405.5
Week 1	431.4
Week 2	119.3
Week 3	28.2
Week 4	15.6
Week 5	12.1
Week 6	9.8
Week 7	8.9
Week 8	9.3
Week 12	7.7
Week 16	10.1
Week 20	8.1
Week 24	6.9

Results

Mean baseline testosterone levels of patients was 405.5 ng/dL. Treatment compliance was good. Only one patients received a depot injection 30 days since the previous monthly injection. Mean testosterone was 431.4 ng/dl, 119.3 ng/dL, 28.2 ng/dL by week 1, 2, 3 and decreased to less than 15.6 ng/dL by week 4 where it remained throughout the treatment period (Table 1). Median time to suppression of serum testosterone was 20.7 days (ranged, 14 to 35 days). Suppression occurred within 1, 2, 3, 4, 5 weeks in 0%, 30.4%, 87.0%, 95.7% and 100% of patients, respectively (Table 2). No transient minor "escape" from suppression occurred in all patients which was defined as a single testosterone value greater than 50 ng/dL once suppression was achieved.

One patients had minor increases (single values) in serum testosterone from the pre-injection value to greater than 50 ng/dL during the stimulation testing following the second depot injection (51 ng/dL 4 h after injection, representing increases of 5 ng/dL from the predose value).

Table 2 Suppression rate of 23 patients within different weeks

Weeks	Suppression number of patients (*n*)	Suppression rate of patients (%)
1	0	0
2	7	30.4
3	20	87.0
4	22	95.7
5	23	100

Thus, the stimulation rate following the second depot injection was 1 of 23 (4.3%). But there was no increases in serum prostate specific antigen or bone pain subsequent to stimulation during the treatment period following suppression in the one patient who had minor increases in serum testosterone during the stimulation testing.

Discussion

The pattern and magnitude of serum testosterone suppression were nearly identical for the monthly (3.75 mg) depot formulation of domestic substitute of leuprorelin acetate microspheres and the same depot formulation of leuprolide acetate with the median time to suppression being 20.7 days in domestic substitute group and 22 days in reported leuprolide acetate group [5]. This monthly depot formulation of domestic substitute of leuprorelin acetate microspheres provided suppression for the duration of the dosing interval as mean testosterone decreased to less than 50 ng/dL by week 3 and to less than 15 ng/dL by week 4 and remained at or below this level at each subsequent regular visit throughout the treatment period, which was the same as results of leuprolide acetate [5, 8]. And determinations performed just before each injection indicated no weakening of the suppressive effect toward the end of the respective dosing intervals. Otherwise, no "escapes" from suppression occurred and no increases in serum PSA or bone pain happened.

Stimulation testing at 4 h intervals up to 12 h after the second depot injection of domestic substitute of leuprorelin acetate microspheres revealed no pattern of testosterone stimulation during chronic dosing with monthly formulation. This result indicates a sufficient degree of pituitary Gn-RH receptor down-regulation after the initial depot injection to prevent any agonistic stimulation of gonadotropin release sufficient to stimulate a clinically meaningful increase in serum testosterone level. Only one patient was observed that there was a minor increases in serum testosterone at 4 h after the second injection during the stimulation testing. However, the maximum of these stimulated values was only 51 ng/dL, indicating that substantial stimulation did occur and but the stimulation rate was very low (4.3%).

These evaluations show that serum testosterone suppression of monthly (3.75 mg) depot formulation of domestic substitute of leuprorelin acetate microspheres is persistent for patients with metastatic prostate cancer. On the other hand, the potential of this formulation of domestic substitute for agonistic stimulation of serum testosterone following a second or more depot injection is obviously weak and is of statistical significance. And even more importantly, these results provide convincing evidence of its clinical efficiency of this depot formulation of domestic substitute of leuprorelin acetate microspheres for serum testosterone suppression during chronic treatment for all patients with prostate cancer.

Conclusion

The monthly (3.75 mg) depot formulation of domestic substitute of leuprorelin acetate microspheres has persistent and strong ability to suppress serum testosterone to and maintain it at a clinically meaningful level. Agonistic stimulation during chronic treatment following subsequent depot injections does not seem to be an issue although it could potentially result in an minor increase in serum testosterone.

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