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Switching of GnRH Agent from Agonist to Antagonist in Patients with Castration-Resistant Prostate Cancer

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Abstract

Objectives: To evaluate the efficacy of alteration from gonadotropin-releasing hormone (GnRH) agonist to antagonist in patients with castration-resistant prostate cancer (CRPC). **Methods:** Fourteen patients with CRPC were switched from GnRH agonist to GnRH antagonist. CRPC was defined as 3 consecutive rises of PSA values under androgen deprivation therapy despite a testosterone level at the castration level. No patient underwent a change in oral anti-androgen agent or any additional therapy. Patients who showed increase of the PSA value within 10% or showed decrease in the PSA value compared to the baseline were defined as responders. We measured serum PSA, testosterone, follicular stimulating hormone (FSH), and leutenizing hormone (LH) at the time of alteration and 3 months after alteration. **Results:** The mean age at diagnosis was 74.8 ± 6.3 years with a mean initial PSA level of 537.3 ± 999.1 ng/mL. The mean age at alteration to GnRH antagonist was 81.4 years with a mean PSA level of 28.6 ng/mL. Two out of 14 patients (14%) were judged as responders based on PSA after alteration to GnRH antagonist, although they did not show any further reduction of the serum testosterone level (remain less than 0.03). Six patients showed further reduction of the serum FSH level after alteration; however, they showed no PSA response (from 46.4 ± 42.6 to 69.4 ± 70.3). **Conclusions:** The switch from GnRH agonist to GnRH antagonist affected 14% of the patients (2 out of 14 patients) with CRPC at 3 months based on PSA. Larger and longer-term studies are required to determine the efficacy of alteration to GnRH antagonist in patients with CRPC.

Keywords

CRPC, GnRH Antagonist, PSA, FSH

1. Introduction

Combined androgen blockade (CAB) with gonadotropin-releasing hormone (GnRH) agonist and anti-androgen is one of the important treatment options for patients with locally advanced or metastatic prostate cancer [1]. Multiple options for secondary treatment have been recommended for patients with castration-resistant prostate cancer (CRPC), such as alternative non-steroidal anti-androgen therapy after the exclusion of anti-androgen withdrawal syndrome, abiraterone [2] [3], enzalutamide [4] [5], low-dose steroid, estrogen preparation, and chemotherapy with docetaxel [6] or cabazitaxel [7].

GnRH antagonist (degarelix), which became clinically available in October 2012 in Japan, quickly binds to GnRH receptors to block their function, subsequently leading to an immediate decrease in testosterone to the castration level without a testosterone surge [8]. It was also reported that GnRH antagonist could extend the duration of PSA recurrence compared with GnRH agonist [9]. Few studies, however, have been reported on the efficacy of change from GnRH agonist to GnRH antagonist in patients with CRPC [10].

In this study, we assessed the utility of change from GnRH agonist to GnRH antagonist in patients with CRPC by measuring sequential changes in the values of PSA, testosterone, follicular stimulating hormone (FSH), and leutenizing hormone (LH).

2. Patients and Methods

This study was approved by the institutional review board at our hospital. Among patients with prostate cancer receiving CAB with GnRH agonist and anti-androgen agent in Nara Prefecture General Medical Center between January 2013 and December 2015, we included patients with CRPC who had been received CAB as the first-line treatment and confirmed anti-androgen withdrawal syndrome after discontinuation of anti-androgen for 4 - 6 weeks.

CRPC was defined as 3 consecutive rises in PSA under androgen deprivation therapy despite testosterone remained at the castration level (less than 0.5 ng/mL) [10]. In the patients, GnRH agonist was altered to GnRH antagonist. Subcutaneous injection of GnRH antagonist was administered as directed in the literature: 240 mg for the first injection, followed by 80 mg every 4 weeks. No patients underwent addition of a low-dose steroids, zoledoronic acid hydrate, or denosumab after switching from GnRH agonist to GnRH antagonist. Patients who changed from anti-androgen agent to abiraterone or enzalutamide simultaneously when switching from GnRH agonist to antagonist, or patients who underwent another additional treatment were excluded from this study. Patients who did not desire to switch GnRH agonist to antagonist were also excluded from this study.

The following data were analyzed: age, PSA, clinical stage and Gleason score at diagnosis, and duration of androgen deprivation therapy. We also measured serum PSA, testosterone, FSH, and LH at the time of change and 3 months after change, respectively. Patients who experienced increase the PSA value within 10% or showed decrease of

PSA value compared to the baseline were defined as responders [10]. The clinical data are presented the mean ± standard deviation.

3. Results

Fourteen patients with CRPC were finally enrolled in this study. Patient characteristics are listed in Table 1. The mean age at the diagnosis of prostate cancer was 74.8 ± 6.3 years, the initial PSA was 537.3 ± 999.1 ng/mL (median: 132.5, range: 12 - 3770 ng/mL), and the ALP was 370.6 ± 369.1 IU/L (median: 273.5, range: 152 - 1512 IU/L). Gleason score was 6 in two, 7 in three, 8 in four, and 9 in two. Three patients had started CAB without prostate biopsy because of high PSA levels (382, 580, and 3770 ng/mL, respectively) and poor physical conditions. Four patients were organ-confined prostate cancer, three were locally-advanced prostate cancer, and remaining seven were metastatic prostate cancer; two with distant lymph node metastasis and five with multiple bone metastasis at the diagnosis. External radiation therapy as the initial treatment had been conducted for 1 patient. The remaining 13 patients had been treated with CAB as the initial treatment. Nine patients were administered leuprorelin acetate and remaining five were administered goserelin acetate as GnRH agonist.

Table 1. Characteristics of the patients with CRPC.

Age at diagnosis (±SD) (years)	74.8 ± 6.3
Initial PSA (ng/mL)	537.3 ± 999 (median: 132, range: 2 - 3770)
Gleason score (case)	
6	2
7	3
8 - 10	6
not done	3
Clinical stage at diagnosis (case)	
B	3
C	3
D	8
Age at alteration (±SD) (years)	81.4 ± 4.3
Duration of agonist (months)	79.6 ± 63.9
PSA before alterarion (ng/mL)	28.6 ± 35.0
PSAV before alteration (ng/mL/year)	43.3 ± 66.4
LH before alteration (mIU/mL)	<0.1
FSH before alteration (mIU/mL)	3.4 ± 2.7
Testosterone before alteration (ng/mL)	<0.03
PSAV: PSA velocity	Mean ± SD

The mean age at change to GnRH antagonist was 81.4 ± 4.3 years, with a mean PSA value of 28.6 ± 35.0 ng/mL at that time. The mean hormonal treatment courses before change to GnRH antagonist were 2.7 ± 1.3 courses and the mean durations of hormonal treatment were 79.6 ± 63.9 months. PSA velocity immediately before change to GnRH antagonist was 43.3 ± 66.4 ng/mL/year. In all 14 patients, testosterone values showed the castration level (less than 0.5 ng/mL) at change. Fourteen percent of patients (2 out of14 patients) were judged as responders to GnRH antagonist based on PSA. PSA changes in One of the two responders showed the decrease of PSA value (from 4.97 to 3.73 ng/mL; −25.0%), and the other showed the increase of the PSA value within 10% (from 3.06 to 3.30 ng/mL; 7.8%). The PSA values in the responders were less than 5 ng/mL at the time of change to GnRH antagonist (4.97 and 3.06 ng/mL, respectively). In all patients, testosterone was maintained at the castrate level (less than 0.5 ng/mL) before and after change. Responders based on PSA did not show any further reduction of testosterone. Six patients showed a further reduction in the serum FSH level, although they did not respond based on PSA. The LH levels were suppressed to below the standard level after change to GnRH antagonist.

Adverse events associated with change to GnRH antagonist were observed in 8 patients (57%). Injection-site reactions were the most frequent adverse events (43%). Painful induration and erythema at the injection site were observed in 4 patients (29%) and 2 patients (14%), respectively, although they disappeared without any treatment within several days after injection. One patient showed high-grade fever after GnRH antagonist injection, which improved without any treatment in a few days.

One of the 2 responders based on PSA has been treated with GnRH antagonist for 20 months without PSA recurrence. The other responder based on PSA discontinued GnRH antagonist administration because of PSA recurrence 6 months after change, and returned to GnRH agonist with an alternative non-steroidal anti-androgen based on the patient's wishes. Five of the 12 non-responders based on PSA continued GnRH antagonist according to their request with an alternative non-steroidal anti-androgen. Six of the 12 non-responders based on PSA returned to GnRH agonist with an alternative non-steroidal anti-androgen after the 3-month evaluation of altered GnRH antagonist. The remaining one patient received chemotherapy with docetaxel. The mean follow-up period was 15.6 ±11.0 months after switching to GnRH antagonist. Within a follow-up period, no one was died with prostate cancer. One patient was died with another cause.

A comparison of patient characteristics between the responders and non-responders based on PSA is presented in Table 2. PSA and the PSA velocity immediately before change were lower in the responder group, although statistical analysis could not be done because of a small number of the responders.

4. Discussion

CAB with a combination of injection of GnRH agonist and an oral anti-androgen is the most utilized modality for advanced or metastatic prostate cancer. However, the efficacy

Table 2. Comparison of characteristics between responders and non-responders.

	Responders (n = 2)	Non-responders (n = 12)
Age at antagonist (years)	81.5 ± 7.8	81.4 ± 4.0
Duration of agonist (months)	80.0 ± 61.0	79.6± 67.1
Mean number of anti-androgen before antagonist	3.5	2.6
PSA velocity (ng/mL/year)	3.4 ± 2.7	49.9 ± 69.8
PSA (ng/mL)		
before	4.0 ± 1.4	32.7 ± 36.3
after	3.5 ± 69.8	64.6 ± 62.4
% change from baseline	−8.5%	123.30%
Testosterone (ng/mL)		
before	<0.03	0.035 ± 0.01
after	<0.03	0.035 ± 0.01
FSH (mIU/mL)		
before	0.48 ± 0.6	3.8 ± 2.6
after	0.56 ± 0.7	2.7 ± 1.9
LH (mIU/mL)		
before	<0.1	<0.1
after	<0.1	<0.1

of CAB is not indefinite, as the castration-resistant status would often appear within 18 - 24 months in patients with advanced prostate cancer [10]. Some secondary treatment options may be proposed for patients with CRPC, such as alternative non-steroidal anti-androgen therapy after the exclusion of anti-androgen withdrawal syndrome, abiraterone [2] [3], enzalutamide [4] [5], low-dose steroid, and estramustine phosphate, and chemotherapy with docetaxel [6] and cabazitaxel [7].

In assessing changes of hormone levels after administering GnRH agonist in patients with prostate cancer, the serum LH level showed an approximately 99% reduction compared with the baseline level, which was maintained for at least 1 year on treatment with GnRH agonist [11]. On the other hand, the serum FSH level decreased to about 75% at 1 month, and showed only an approximately 55% reduction compared with the baseline level after one-year treatment with GnRH agonist [11]. GnRH antagonist (degarelix) facilitates a prompt decrease in testosterone to the castration level without testosterone surge [1]. It was also reported that GnRH antagonist could extend the duration of PSA recurrence compared with GnRH agonist [9]. However, there have been few reports demonstrating the efficacy of switching of GnRH agent from agonist to antagonist in patients with CRPC. GnRH antagonist rapidly achieves an approximately

90% reduction of FSH from the baseline level within 1 month, and maintains suppression for 1 year [11] [12]. Furthermore, GnRH antagonist showed further suppression of FSH in patients who switched from GnRH agonist to GnRH antagonist as well as that observed during continuous GnRH antagonist treatment [12].

According to immunohistochemical and immunoblotting examinations, FSH receptors were selectively expressed on the surface of blood vessels of the prostate [13]. Furthermore, FSH may affect the pathogenesis and progression of prostate cancer [14].

We hypothesized that GnRH antagonist is effective for patients with CRPC through a further reduction of FSH. In our study, GnRH agonist was switched to GnRH antagonist in patients with CRPC, and 14% of patients (2 out of 14 patients) with CRPC were judged as responders based on PSA. Miller *et al.* [15] reported that 4 out of 25 patients (16%) responded to GnRH antagonist as second-line hormonal therapy, who had been initially treated with leuprorelin acetate, and experienced PSA progression. Alexandra *et al.* [10] also reported that 4 out of 27 patients (23%) responded based on PSA at 3 months after switching from GnRH agonist to GnRH antagonist. Thus, change to GnRH antagonist might be effective in some cases.

Alexandra *et al.* [10] hypothesized that change of GnRH agonist to antagonist could be efficient through further reduction of testosterone and FSH. In fact, PSA responders in their study showed the further reduction of testosterone. In our study, however, 2 non-responders based on PSA showed further reduction of testosterone. Since all of our patients had already reached the castration level before change to GnRH antagonist, this was probably the reason why GnRH antagonist barely reduced the testosterone level any further. It was recommended that serum testosterone should be maintained at less than 0.2 ng/mL in advanced prostate cancer patients receiving androgen deprivation therapy [16] [17]. Serum testosterone levels in our study were reduced to less than 0.2 ng/mL in all patients before and after change to GnRH antagonist.

Further reduction of FSH was observed in 6 patients after swiching to GnRH antagonist, although they were non-responders based on PSA. Further studies are necessary to investigate the relationship between the serum FSH level and the cancer progression in patients with CRPC.

de la Rosette *et al.* [11] demonstrated the progression of prostate cancer after switching from GnRH agonist to GnRH antagonist. Five out of 134 patients (3.7%) showed the progression of prostate cancer: 4 (2.9%) had metastatic prostate cancer, and the remaining patient had locally advanced prostate cancer. All 5 patients had high baseline PSA levels (619 - 10,952 ng/mL). This suggests that it might not be able to provide additional benefits for those with advanced prostate cancer.

Recently, Fitzpatrick *et al.* [18] described that it is important to evaluate the therapeutic efficacy not only PSA value but imaging studies within 3-months after initiation of treatment in patients with CRPC. In this study, however, we did not evaluate the therapeutic efficacy with imaging studies in all of the patients, and we defined patients as responders only who experienced a change in the PSA value within 10% or showed decrease of PSA compared to the baseline.

In our study, there was no difference between responders and non-responders except for PSA and the PSA velocity immediately before change, although statistical analysis could not be done because of a small number of responders. PSA and the PSA velocity were lower in the responder group than in the non-responder group (4.0 ± 1.4 vs. 32.7 ± 36.3 ng/mL and 3.4 ± 2.7 vs. 49.9 ± 69.8 ng/mL/year, respectively) (Table 2). High PSA values and high PSA velocities indicate advanced prostate cancer, and our results suggest that these 2 parameters could be prognostic factors to predict the efficacy of change to GnRH antagonist in patients with CRPC.

Treatment options are limited in patients with CRPC. Although the effects were limited only based on PSA in our study, it appears that switching from GnRH agonist to GnRH antagonist could be one of the treatment options because it might facilitate the control of prostate cancer progression in some cases, and could delay the induction of chemotherapy with docetaxel and cabazitaxel.

The limitations of this study are the very small number of patients and relatively short duration of follow-up. Additional number of patients with CRPC are needed to evaluate sequential changes in the values of PSA, testosterone, FSH and LH after switching from GnRH agonist to antagonist. Because there have been few studies reporting the effects of switching from GnRH agonist to GnRH antagonist on patients with CRPC, further prospective studies are required to evaluate the efficacy of change to GnRH antagonist, and to verify if PSA and the PSA velocity immediately before change could be used to predict the efficacy of change. In addition, further studies are necessary to determine whether change to GnRH antagonist could be a second-line hormone therapy for patients with CRPC.

5. Conclusion

The change from GnRH agonist to GnRH antagonist affected 14% of patients (2 out of 14 patients) with CRPC at 3 months based on PSA values. Larger and longer-term studies are necessary to evaluate the efficacy of change to GnRH antagonist.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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