Clinical Effect of Switching from a Luteinizing Hormone-Releasing Hormone Agonist to an Antagonist in Patients with Castration-Resistant Prostate Cancer and Serum Testosterone Level ≥ 20 ng/dl

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Introduction: The efficacy of conversion from a luteinizing hormone-releasing hormone agonist to an antagonist was evaluated prospectively in patients with castration-resistant prostate cancer. Materials and Methods: From October 2012 to December 2014, 8 cases with a serum testosterone level ≥ 20 ng/dl during following androgen deprivation therapy were enrolled and received degarelix monthly. The primary end-point goal was to determine the effective prostate-specific antigen response rate. The secondary end-point goal was to assess the proportion of cases with a decrease in serum testosterone level to < 20 ng/ml. Results: One patient achieved a complete response, with a prostate-specific antigen level of 0.02 ng/ml at the nadirend of the study. The effective response rate was 25.0% (2/8), and the proportion of cases with prostate-specific antigen decline was 62.5% (5/8). In 5/8 cases (5/8, 62.5%), serum testosterone levels declined to < 20 ng/dl. Conclusion: Switching to a luteinizing hormone-releasing hormone antagonist in patients with testosterone levels ≥ 20 ng/dl may be an option in sequential androgen deprivation therapy for some patients.
Traditionally, castrated serum testosterone level is defined as < 50 ng/dl [1], however, a lower level (< 20 ng/dl) of serum testosterone contributes to a better prognosis [4]. During treatment with an LH-RH agonist, if a lower serum testosterone level (< 20 ng/dl) is not achieved, 2 options remain for treatment: surgical castration [5] or switching to an LH-RH antagonist.

Recently, the use of an LH-RH antagonist was shown to reduce the serum testosterone level and to control the progression of PCa compared to the use of an LH-RH agonist [6, 7]. In addition, several reports [8, 9] demonstrated that conversion to an LH-RH antagonist had the potential to control progression. Because no prospective study has been done, the long-term effects and optimal candidates that will respond effectively when switching to an LH-RH antagonist are uncertain.

In this study, we evaluated the efficacy of conversion to an LH-RH antagonist prospectively in patients with CRPC. The optimal candidates to enroll using this strategy were determined based on an entry criterion of serum testosterone level ≥ 20 ng/dl.

### Methods

We used the sequential injection of an LH-RH agonist (leuprolide acetate or goserelin), along with a non-steroidal anti-androgen (bicalutamide or flutamide) followed by estramustine for...

| Patient demography       | Value |
|--------------------------|-------|
| Number                   | 8     |
| Age (range)              | 72.7±4.5 (64-80) |
| Staging at diagnosis     |       |
| B                        | 1     |
| C                        | 1     |
| D1                       | 2     |
| D2                       | 4     |
| Gleason score            |       |
| 6                        | 1     |
| 7                        | 2     |
| 8                        | 5     |
| Treatment history        |       |
| RT + ADT                 | 1     |
| RP + ADT                 | 2     |
| ADT                      | 5     |
| Combined drug            |       |
| Estramustine             | 2     |
| Bicalutamide             | 2     |
| Flutamide                | 1     |
| None                     | 3     |

ADT = Androgen deprivation therapy; RT = radiation therapy.

Fig. 1. Trend of serum PSA level after administration with LH-RH antagonist (Open circle: date of PD)
ADT. All cases met the modified CRPC criteria [1, 10], described as a castrated serum testosterone level (< 50 ng/dl), three consecutive rises of prostate specific antigen (PSA) that are 1 week apart and result in 2, 50% increases over the baseline with each increase in PSA > 2.0 ng/ml, no response to anti-androgen withdrawal for relevant cases, and PSA progression with consecutive hormonal manipulations and progression of osseous lesions. 8 cases that met the criterion of a serum testosterone level ≥ 20 ng/dl were enrolled in this study. The institutional review board approved the study, and all patients gave their full informed consent.

 Patients received the LH-RH antagonist degarelix monthly, with 240 mg as the first dose and 80 mg for subsequent doses, subcutaneously. The PSA level and the testosterone level were measured during treatment to determine the PSA response, as described below.

The percent PSA decrease compared with baseline was calculated. A complete response (CR) was defined as a PSA level below the normal range (4 ng/ml); a partial response (PR) was defined as a PSA reduction > 50%, stable disease (SD) was defined as a PSA reduction < 50%, and progressive disease (PD) was defined as three consecutive increases in PSA > 2.0 ng/ml. The date of progression was defined as the first date that the PSA increased > 2.0 ng/ml, followed by two sequential rises in PSA.

Following the completion of every 3 treatments, patients were evaluated for response with computed tomography or bone scintigraphy. If radiologic disease progression (new metastasis or > 25% progression of the targeted lesion) was observed, the patient was classified as having PD. This study was continued until patients developed PD as determined by PSA progression or radiological progression.

The primary goal was to determine the effective PSA response rate to the LH-RH antagonist. The secondary goal was to assess the proportion of cases with a serum testosterone level < 20 ng/dl after 3 months.

Results

From October 2012 to December 2014, 8 PCa cases matched the study criteria and were enrolled. The demographic characteristics of these 8 patients are summarized in table 1. At the start of LH-RH antagonist treatment, 5 cases received anti-androgens or estramustine continuously. Three cases received no additional drugs.

After LH-RH antagonist administration, 1 case was diagnosed as a CR and was associated with a PSA level of 0.02 ng/ml which was maintained for 12 months. Another case was diagnosed as a PR, and another 3 cases were diagnosed as SD. The effective response rate was 25.0% (2/8 cases), and the proportion of patients with PSA decline was 5/8 cases (62.5%). The other 3 cases developed PD. No patient had to stop treatment before determination of PSA progression due to side effects or radiological PD (fig. 1).
PSA response was also compared to the Gleason score. 2 cases with a Gleason score of 6 were classified as CR and SD, 2 cases with a Gleason score of 7 were classified as SD, and 4 cases with a Gleason score ≥ 8 were classified as PD, except for 1 PR case.

We compared the serum testosterone levels prior to enrollment and 3 months after drug administration. In 5/8 cases (62.5%), serum testosterone levels were < 20 ng/dl (lower testosterone group). In contrast, in 3/8 cases (37.5%), serum testosterone levels remained > 20 ng/dl (higher testosterone group) (Fig. 2). The lower testosterone group consisted of 1 case with a CR, 1 case with a PR, 2 cases with SD, and 1 case with PD. 2 cases with PD and 1 case with SD were in the higher testosterone group.

Discussion

During ADT for PCa, treatment options include an LH-RH agonist, an anti-androgen, and an LH-RH antagonist. A sequential treatment strategy is starting to be evaluated [7, 11], but the optimal order to administer these options remains controversial.

To establish a strategy to determine the optimal order of these ADT options, monitoring of the serum testosterone level is imperative, since a lower serum testosterone level may contribute to a better prognosis [4]. In this study, we focused on patients with CRPC with a serum testosterone level ≥ 20 ng/dl, and the effectiveness of a switch to an LH-RH antagonist was evaluated prospectively. Surprisingly, the effective response rate was 25% (2/8), and 62.5% of cases (5/8) had PSA declines.

According to a previous report [9], among 17 cases that switched to an LH-RH antagonist, only 1 case (6%) achieved a CR or PR, and 4 cases (23%) were recognized as PSA responders; these rates were lower than in our study (6% versus 25%, respectively, and 23% versus 62.5%, respectively). We suspect that the main reason for the differences between these results was due to the background of the enrolled cases. In our prospective study, the criterion of a serum testosterone level of ≥ 20 ng/dl was adapted before the cases were enrolled, but this was not a requirement in the previous report [9].

In terms of the relationship between PSA response and testosterone decline, all of the responders had a decline in testosterone level in the previous study [9]. Our study supported those results since 5 of the 6 cases (83.3%) in the lower testosterone group were responders. Another report [8] demonstrated that switching to an LH-RH antagonist drastically reduced PCa progression in a case with an insufficient decrease in testosterone level (68 ng/dl) induced by an LH-RH agonist. Thus, the decrease in the testosterone level induced by an LH-RH antagonist may be a factor involved in PCa progression.

The mechanism of LH-RH antagonist action in CRPC remains unknown. Hypothesized mechanisms are inadequate systemic delivery and production of GnRH agonist antibody, resistance of pituitary cells to a GnRH agonist, mutation of the GnRH receptor, [8] and a direct effect through the receptor [12]. In addition, another report indicated a correlation of LH-RH antagonist treatment with follicle-stimulating hormone [13].

Enzalutamide [14] and abiraterone [15] are new drugs with effective clinical outcomes during sequential ADT that have recently become available. Although additional drugs for ADT can be managed, their optimal usage remains uncertain. Administration of each drug should be optimally timed for candidate patients while monitoring predictive factors to achieve the greatest delay of cancer progression.

Our study had several limitations, such as a small number of cases with different treatment backgrounds. However, we found that a pre-enrollment testosterone level ≥ 20 ng/dl after receipt of an LH-RH agonist for CRPC may be a crucial predictor of patients that will have a positive response when switching to an LH-RH antagonist during sequential ADT.

Our results suggest that the testosterone level in patients with CRPC may provide a candidate index for identifying those who would benefit from a switch to an LH-RH antagonist during ADT.
References

1. Mottet N, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, Schmid HP, van der Kwast T, Wiegel T, Zattoni F, Heidenreich A: EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. Actas Urol Esp 2011;35:565–579.

2. Di Lorenzo G, Buonerba C, Autorino R, De Placido S, Sternberg CN: Castration-resistant prostate cancer: current and emerging treatment strategies. Drugs 2010;70:983–1000.

3. Soga N, Hori Y, Ogura Y, Hayashi N, Sugimura Y: The long-term results with delayed-combined androgen blockade therapy in local or locally advanced prostate cancer. Jpn J Clin Oncol 2012;42:534–540.

4. Morote J, Orsola A, Planas J, Trilla E, Ravenotos CX, Cecchini L, Catalan R: Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. J Urol 2007;178:1290–1295.

5. Oefelein MG, Feng A, Scolieri MJ, Ricchiutti D, Resnick MI: Reassessment of the definition of castrate levels of testosterone: implications for clinical decision making. Urology 2000;56:1021–1024.

6. Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, Jensen JK, Olesen TK, Schroder FH: The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int 2008;102:1531–1538.

7. Crawford ED, Tombal B, Miller K, Boccon-Gibod L, Schroder F, Shore N, Moul JW, Jensen JK, Olesen TK, Persson BE: A phase III extension trial with a 1-arm crossover from leuprolide to degarelix: comparison of gonadotropin-releasing hormone agonist and antagonist effect on prostate cancer. J Urol 2011;186:889–897.

8. Raddin RS, Walko CM, Whang YE: Response to degarelix after resistance to luteinizing hormone-releasing hormone agonist therapy for metastatic prostate cancer. Anticancer Drug 2011;22:299–302.

9. Masson-Lecomte A, Guy L, Pedron P, Buryere F, Roupret M, Nsabimura Y, Dahan M, Hoffman P, Salomon L, Vardos D, Hoznek A, Le Corvoisier P, Morel P, Abbou C, de la Taille A: A switch from GnRH agonist to GnRH antagonist in castration-resistant prostate cancer patients leads to a low response rate on PSA. World J Urol 2013;31:339–343.

10. Cookson MS, Roth BJ, Dahm P, Engstrom C, Freedland SJ, Hussain M, Lin DW, Lowrance WT, Murad MH, Oh WK, Penson DF, Kibel AS: Castration-resistant prostate cancer: AUA Guideline. J Urol 2013;190:429–438.

11. de la Rosette J, Davis R, 3rd, Frankel D, Kold Olesen T: Efficacy and safety of androgen deprivation therapy after switching from monthly leuprolide to monthly degarelix in patients with prostate cancer. Int J Clin Pract 2011;65:559–566.

12. Fahrenholtz CD, Rick FG, Garcia MI, Zarandi M, Cai RZ, Block NL, Schally AV, Burnstein KL: Preclinical efficacy of growth hormone-releasing hormone antagonists for androgen-dependent and castration-resistant human prostate cancer. Proc Natl Acad Sci USA 2014;111:1084–1089.

13. Beer TM, Garzotto M, Eilers KM, Lemmon D, Wessinger EM: Targeting FSH in androgen-independent prostate cancer: abarelix for prostate cancer progressing after orchietomy. Urology 2004;63:342–347.

14. Loriot Y, Miller K, Sternberg CN, Fizazi K, De Bono JS, Chowdhury S, Higano CS, Nooneberg S, Holmstrom S, Mansbach H, Perabo FG, Phung D, Ivanescu C, Skaltsa K, Beer TM, Tombal B: Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. Lancet Oncol 2015;16:509–521.

15. Sidaway P: Prostate cancer: Abiraterone treatment improves overall survival in patients with mCRPC. Nat Rev Urol 2015;12:120.