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ORIGINAL ARTICLE

Efficacy of switching therapy of luteinizing hormone–releasing hormone analogue for advanced prostate cancer

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Abstract This study was conducted to determine the efficacy of switching therapy with a second-line luteinizing hormone–releasing hormone (LHRH) analogue after prostate-specific antigen (PSA) progression for advanced prostate cancer. We enrolled 200 patients, from December 2005 to September 2013, with nodal positive, metastatic prostate cancer or disease progression after definite treatment receiving continuous LHRH analogue therapy with monthly depot leuprorelin(sc) acetate 3.75 mg/vial (LA) or goserelin acetate(sc) 3.6 mg/vial (GA). If the patients had castration-resistant prostate cancer, the treatment choice of switching therapy (from LA to GA or from GA to LA) prior to starting chemotherapy was given. The LH, testosterone level, and PSA change were recorded. The records showed that there were 127 patients receiving LA as initial ADT therapy, whereas the other 73 patients were in GA therapy. A total of 92 patients received LHRH analogue switching therapy (54 patients switched from LA to GA and 38 switched from GA to LA). The effect of LH and testosterone reduction prior to and after switching therapy was comparable between the two groups, and increased PSA level after 3 months of treatment was seen in both groups (median PSA: 15.7–67.7 ng/mL in the LA to GA group; 15.2–71.4 ng/mL in the GA to LA group). This study concluded that switching therapy for patients with PSA progression after ADT has no efficacy of further PSA response.

Conflicts of interest: All authors declare no conflicts of interests.

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Introduction

Androgen deprivation therapy (ADT) with luteinizing hormone–releasing hormone (LHRH) analogue has been the standard treatment for advanced prostate cancer since the demonstration of the hormone dependence of prostate cancer cells. In the past 20 years, medical castration with the use of LHRH analogue has been proved as a tolerated and effective option for advanced prostate cancer because of its survival benefits [1–4]. It has also become the replacement for surgical castration (bilateral orchiectomy) because of its convenience and avoidance of body integrity loss.

ADT with LHRH analogues decreases PSA and improves clinical symptoms in about 90% of patients. However, limitation in the duration of response for the drug exists and after that castration-resistant prostate cancer (CRPC) develops. Different LHRH analogues are considered equivalent [4–6], so there was no rule about changing one LHRH analogue to another in the former concept prior to starting therapy for CRPC. However, various agents have different chemical structures, so it is possible that they could result in different patient responses. A study from multiple institutions in Canada demonstrated the efficacy of second-line LHRH analogues after disease progression [7]. They showed PSA decrease after switching therapies, and the decrease was more significant in the group switching from leuprolide acetate (LA) to goserelin acetate (GA). According to the hypothesis of divergent way of action from various LHRH analogues and the possible efficacy of switching therapy, we performed this study to determine if changing LHRH analogues would lead to PSA response.

Methods

Patient selection, treatment, and follow-up

We performed a prospective study from December 2005 to September 2013 in a single medical institute. We identified patients with initially diagnosed nodal positive (N1), metastatic (M1) prostate cancer and disease progression after definite treatment including radical prostatectomy and radiotherapy. The patients received continuous LHRH analogue therapy as the initial ADT with Depot leuprorelin(sc) acetate 3.75 mg/vial (LA) or goserelin acetate(sc) 3.6 mg/vial (GA) every month, and the concomitant nonsteroidal antiandrogen was only allowed for 1–4 weeks when we initiated ADT to avoid flare-up phenomenon. Other patients receiving hormonal manipulation such as diethylstilestrol, steroidal antiandrogen, or ketaconazole were excluded. Furthermore, if patients had met the criteria of CRPC, defined as two consecutive PSA increases while on ADT and reaching castration testosterone level ($<$ 0.2 ng/mL), we gave these patients the choice of switching therapy from the original LHRH analogues to another regimen (LA to GA or GA to LA) prior to starting chemotherapy treatment. The second-line LHRH analogue was used for at least 3 months to determine the PSA response. Baseline data including patient demographics, initial TNM stage, baseline PSA, and Gleason score were collected. The LH, testosterone, and PSA level were checked every 3 months and whether patients could reach the cutoff value (LH $<$ 1.0 mIU/mL and testosterone level $<$ 0.2 ng/mL or $<$0.1 ng/mL) was determined at the first 3-month follow-up. The PSA level prior to switching therapy and every 3 months after the therapy were recorded to analyze the treatment response. This study was approved by the CGMH Institutional Review Board.

Statistical analysis

The baseline demographic data of patients and the efficacy of lowering hormone level were analyzed with Fisher's exact test, Pearson's Chi-square test, and two-tailed independent *t* test. McNemar test, Wilcoxon signed rank test, and Mann–Whitney *U* test were used to show the significance of LH or testosterone change and PSA response. All analyses were carried out using SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

From December 2005 to September 2013, a total of 200 patients met the inclusion criteria. The baseline data of patients are shown in Table 1. Overall, 127 patients received LA as the initial ADT therapy and the other 73 patients were in GA therapy. There was no statistical difference in terms of age, initial TNM stage, Gleason score, or baseline PSA between the groups of patients receiving LA or GA. The efficacy of reducing LH less than 1.0 mIU/mL (73.2% in LA and 74% in GA group; $p = 0.909$) and testosterone less than 0.2 ng/mL (81.9% in LA and 80.8% in GA group; $p = 0.851$) was equivalent. As regards the extremely low testosterone level of less than 0.1 ng/mL (the lowest sensitive level in our clinical laboratory according to the new rapid polyelectrolyte-based immunofiltration technique [8]), there were 49.6% patients in the LA group and 47.9% patients in the GA group who could reach this level.

Switching therapy

In the study population, there were 92 patients included in the switching therapy with the available clinical data. Fifty-

Table 1 Baseline patient characteristics.

		Leuprorelin No. (%)	Goserelin No. (%)	*p*
N		127	73	
Age (y)		77.1 ± 8.5	76.7 ± 8.4	0.757
Initial PSA (ng/mL)		404.1 ± 1293.2	583.3 ± 1689.2	0.413
Gleason score	2–4	2 (1.8)	1 (1.6)	0.249
	5–7	54 (49.5)	24 (38.1)	
	8–10	53 (48.6)	38 (60.3)	
Initial T stage	1	9 (9.1)	4 (7.4)	0.198
	2	22 (22.2)	5 (9.3)	
	3	52 (52.5)	36 (66.7)	
	4	16 (16.2)	9 (16.7)	
Initial stage	1	5 (5.2)	1 (1.9)	0.113
	2	16 (16.7)	3 (5.8)	
	3	34 (35.4)	17 (32.7)	
	4	41 (42.7)	31 (59.6)	

PSA = prostate-specific antigen.