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Original Article

Surgical castration efficiently delays the time of starting a systemic chemotherapy in castration-resistant prostate cancer patients refractory to initial androgen-deprivation therapy

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ABSTRACT

Background: The aim of this study was to investigate the effects of surgical castration, particularly delaying the time to entrance of systemic chemotherapy, in castration-resistant prostate cancer (CRPC) patients who were refractory to initial combination androgen deprivation therapy.

Materials and methods: We analyzed the clinical data of 14 CRPC patients diagnosed at Seoul National University Bundang Hospital (SNUBH) from November 2008 through May 2015. After exclusion of three patients, we finally analyzed the baseline characteristics of 11 CRPC patients. We also assessed the delaying time of docetaxel administration, which was defined as response duration, after surgical castration.

Results: After bilateral orchiectomy, the treatment response rate was 45.4% and the median duration of response was 9 months (range 4–48 mo). Responders had less aggressive biopsy Gleason scores compared to nonresponders. Notably, responders showed the reducing pattern of serum prostate specific antigen levels, while nonresponders demonstrated increasing tendency after surgical castration. Moreover, responders also presented with a reduction pattern of serum testosterone levels, whereas nonresponders showed an increasing pattern of testosterone levels after bilateral orchiectomy.

Conclusions: In summary, despite the limited number of cases for convincing evidence, our results shed light again on the clinical benefits of surgical castration prior to the systemic chemotherapy in some CRPC patients after initial hormone therapy.

1. Introduction

Castration-resistant prostate cancer (CRPC) is a clinically significant disease due to its aggressiveness and lack of curative treatment modalities.[1] Prior to development of CRPC, patients are initially treated with androgen deprivation therapy (ADT) such as luteinizing hormone-releasing hormone (LHRH) agonists and antiandrogen agents.[2] In CRPC various therapeutic agents can be adopted, including androgen receptor targeted drugs, taxane chemotherapy and immunotherapy.[3] Among these, taxane-based chemotherapy such as docetaxel is regarded as a final treatment option for CRPC patients with improvement of survival outcomes.[4,5] However, survival gain of taxane-based chemotherapy is not substantial—less than 4–5 months[6]—and therefore; physicians and researchers have struggled to develop new therapeutic strategy to delay the time of administration of chemotherapy as much as possible.

According to the contemporary guidelines, CRPC is initially responsive to second-line hormone therapy, such as ketoconazole and antiandrogen withdrawal, whereas hormone-refractory prostate cancer is eventually not responsive to any hormone manipulation.[1,7–9] In this regard, controlling androgen or testosterone levels appropriately is an important issue in CRPC patients to determine further therapeutic strategy.[10] Surgical castration (bilateral orchiectomy) and medical castration (LHRH agonists) are the mainstays for achieving castrate testosterone levels.[11] However, LHRH agonists cannot induce the complete castration levels of testosterone in some patients.[12] Instead, surgical castration can completely eliminate remaining testosterone produced by the Leydig cells in testes.[13]

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In this study, we assessed the effects of surgical castration, particularly delaying the time to entrance of systemic chemotherapy, in CRPC patients who were refractory to initial combination ADT.

2. Material and methods

2.1. Study population

We reviewed the clinical data of 14 CRPC patients diagnosed at Seoul National University Bundang Hospital (SNUBH) from November 2008 through May 2015. We defined castration-resistant prostate cancer if the patients showed disease progression despite a castrate testosterone level less than 50 ng/dL, presented with three consecutive rises of serum prostate-specific antigen (PSA) above nadir, and if there was radiological/clinical progression on androgen blockade therapy.[14] Among these, 3 patients were excluded from analysis due to follow-up loss. Thus, we finally analyzed 11 patients with CRPC who underwent bilateral orchiectomy. The Institutional Review Board at SNUBH approved our study.

2.2. Study design

We examined the baseline characteristics of 11 patients with CRPC as follows: age, initial serum PSA, biopsy Gleason score (GS), type of ADT, and duration of ADT. We also measured the serum PSA and testosterone levels before and after bilateral orchiectomy, serum PSA levels at nadir status, and duration of PSA nadir, by obtaining blood samples from CRPC patients. We performed the bilateral subcapsular orchiectomy with epididymal sparing according to the standard protocol.[15] There were no substantial complications related to surgery. We finally assessed the delaying time of docetaxel administration (or response duration) after surgical castration. We divided patients into two groups (responder and nonresponder) according to the treatment responses to surgical castration. Treatment response was defined if the delaying time to docetaxel treatment was more than 3 months. According to the routine follow-up protocol of our hospital, we monitored serum PSA levels every 1–2 months.

3. Results

The clinical characteristics of 11 CRPC patients who underwent bilateral orchiectomy after combined ADT are summarized in Table 1. Among these, treatment responses to surgical castration were found in 5 patients (response rate 45.4%). Of note, in the responder group with delaying time of docetaxel treatment, the median duration of response was 9 months (range 4–48 mo). Although initial serum PSA levels were variable among patients, the responder group had less aggressive biopsy GS compared to nonresponders. While most responders had biopsy GS 8(4 + 4) and only one patient had GS 9(4 + 5), there were two patients of GS 10(5 + 5), one patient of GS 9(4 + 5), and two patients of GS 8(4 + 4) in the nonresponder group. Median duration of ADT was similar between responder and nonresponder groups (22 mo vs. 24 mo, respectively)

Notably, the responsiveness of serum PSA and testosterone levels after bilateral orchiectomy were different between responders and nonresponders (Fig. 1). Responders showed the reducing tendency of serum PSA levels, while nonresponders demonstrated increasing tendency after surgical castration (Fig. 1A). Moreover, responders also presented a reduction pattern of serum testosterone levels, whereas nonresponders showed an upregulating pattern of testosterone levels after bilateral orchiectomy (Fig. 1B). These results indicate that surgical castration can offer the clinically beneficial effects, such as delaying the time to chemotherapy, on CRPC patients who are refractory to initial ADT.

4. Discussion

For treating metastatic prostate cancer, there are four types of androgen deprivation therapy (ADT), including simple orchidectomy, LHRH agonists, anti-androgens, and gonadotrophin releasing hormone (GnRH) antagonists.[16] Among these, LHRH agonists are primarily regarded as the first line therapy of ADT since it was first introduced in the early 1980s.[17] In the mechanistic view of ADT on prostate cancer, optimal testosterone control is the important issue in patients receiving ADT.[18] Although these agents are an alternative therapeutic modality to surgical castration with similar overall survival benefits, suboptimal testosterone control is the critical drawback in a significant number of patients.[18–23] For example, Oefelein et al[21] reported that 13% of prostate cancer (PCa) patients treated with LHRH agonists failed to achieve castrate level of testosterone (20 ng/dL). In the cross-sectional study by Morote et al,[23] approximately 11% of advanced PCa patients managed by LHRH agonist did not eventually achieve the castrate testosterone levels. In this regard, some patients who have relapsed disease after initial treatment with LHRH agonists may significantly show the clinical and biochemical responses to surgical castration. For example, a recent case report demonstrated that two CRPC patients who were resistant to LHRH agonists demonstrated good responses to bilateral orchiectomy, resulting in decreases of serum PSA and clinical improvement.[24] However, there is still little evidence of the potential benefits of surgical castration in the patients who are resistant to medical castration.

Table 1
Baseline characteristics of men with castration-resistant prostate cancer undergoing bilateral orchiectomy.

Group[a)]	Age (y)	Initial PSA (mg/mL)	Biopsy GS	ADT type	ADT duration (mo)	PSA (ng/mL) at ox	1st PSA (ng/mL) after ox	T (ng/dL) at ox	1st T (ng/dL) after ox	DCT	Delaying time (mo)
Responders	68	378.0	8 (4 + 4)	G & B	13	103.2	87.3	16	13	Not yet	13
	66	17.4	8 (4 + 4)	G & B	17	9.1	6.1	17	5	Not yet	6
	64	16.7	—	G & B	24	12.7	12.6	18	12	Not yet	4
	73	51.0	8 (4 + 4)	G & B	22	8.1	7.7	9	7	Not yet	9
	70	78.3	9 (4 + 5)	G & B	41	133.2	—	—	—	Not yet	48
Nonresponders	53	>100	8 (4 + 4)	L & B	13	28.8	28.2	6	12	Add	1
	72	—	—	G & B	9	379.2	578	22	34	Add	0
	65	75.1	10 (5 + 5)	G & B	24	103.9	195.3	34	15	Add	0
	65	32.3	9 (4 + 5)	G & B	24	52.6	79.2	11	5	Add	0
	68	17.0	8 (4 + 4)	G & B	50	14.8	24.5	9	11	Add	1
	78	91.0	10 (5 + 5)	G & B	69	91.4	81.2	19	75	Add	1

[a)] Cases are divided into two groups (responder and nonresponder) according to the treatment responses to surgical castration.
ADT, androgen deprivation therapy; B, biclutamide; C, cyproterone acetate; DCT, docetaxel; G, goserelin acetate, GS, Gleason score; L, leuprorelin acetate; ox, bilateral orchiectomy; PSA, prostate-specific antigen; T, testosterone.