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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.

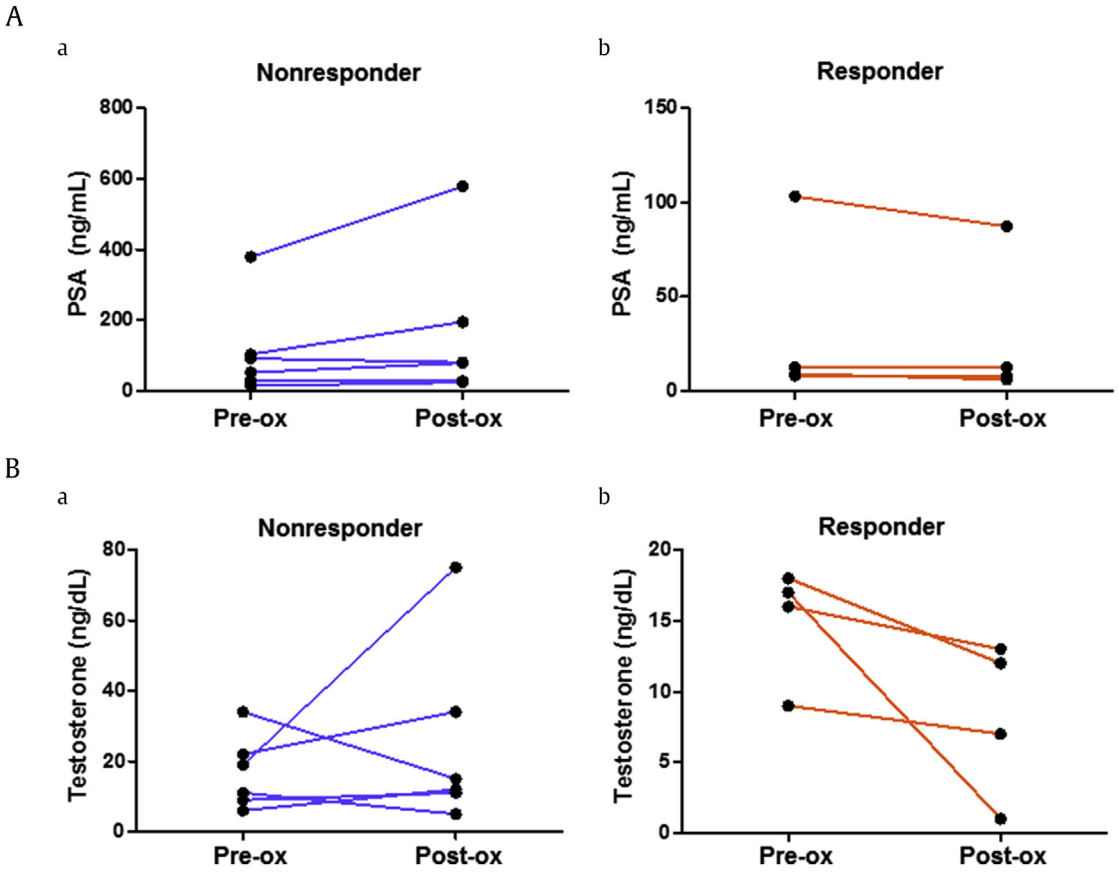

Fig. 1. Clinical responsiveness of patients with castration-resistant prostate cancer by surgical castration. (A) Serum prostate-specific antigen (PSA) levels before (nonresponder) and after (responder) bilateral orchiectomy. (B) Serum testosterone levels before (nonresponder) and after (responder) bilateral orchiectomy. PSA and testosterone values of nonresponder and responder group are represented with blue and orange lines, respectively. Ox, orchiectomy; PSA, prostate-specific antigen.

In the present study, one key observation was that the responder group (approximately 50% of patients) showed the time delaying of docetaxel treatment with reducing pattern of PSA after bilateral orchiectomy compared to the nonresponder group. This means that surgical castration may be effective for controlling disease status in some CRPC patients who are resistant to initial ADT. Similar to our findings, there are potential hypotheses to explain the beneficial effects of surgical castration in the patients who are refractory to initial ADT. First, some patients who are resistant to LHRH-agonists may not achieve the castrate testosterone levels after sufficient treatment duration by unknown mechanisms in the hypothalamo–pituitary–gonadal axis.[13] Second, other patients who are resistant to LHRH-agonists present with serum testosterone levels decreased to castration levels by definition; however, testosterone cannot be diminished low enough under clinically hormone-refractory states. Therefore, insufficient reduction of serum testosterone may upregulate the expression of androgen receptor and its target genes and eventually stimulate the oncogenic signaling pathways despite the low level of serum testosterone.[25] Third, the residual Leydig cells in hormonal treatment-induced atrophic testes may act as functional units, which are responsible for the testosterone resurgence and the failure of LHRH agonist therapy. Indeed, Leydig cell hyperplasia was a poor predictive sign for treatment response of LHRH agonists in the study by Olaopa et al.[24] They noted that two patients demonstrated a substantial response to bilateral orchiectomy for Leydig cells ablation, while one patient who had small amounts of Leydig cells showed a poor response to surgical castration.[24]

Another important observation was that the responder population presented a reduction pattern of serum testosterone levels after bilateral orchiectomy, whereas the nonresponder population demonstrated upregulating tendency even after surgical castration. Because testosterone levels of both responders and nonresponders were lower than 20 ng/dL after initial ADT, previously described hypotheses related to suboptimal castration levels and Leydig cells hyperplasia cannot explain the results. Instead, Mostaghel et al[26] recently suggested that intraprostatic androgens and their target gene expression can be the potential mechanism of the insufficient responses of medical ADT despite the castrate serum testosterone levels. That is, medical castration dependent on serum testosterone cannot fully represent the androgen status within the prostate tissue harboring cancer. They hypothesized that suboptimal reduction of intraprostatic testosterone and resultant activation of androgen-regulated genes can render prostate cancer cells to adapt to survive in a low-testosterone microenvironment.[26] Gregory et al[27] also suggested that metabolic adaptation of prostate cancer cells may contribute to the resistance to hormonal treatments, and thus therapeutic strategy for repressing substantially the tumoral androgen activity should be required.[27] In this context, we believe that surgical castration can be considered as a potential therapeutic option prior to docetaxel treatment in metastatic CRPC patients who are resistant to initial ADT, particularly with castrate serum testosterone levels. To achieve the optimal clinical efficacy by surgical castration in these patients, novel tools for measuring intraprostatic androgen status should be developed to select appropriate patients.

We should acknowledge several critical limitations in the present study. First, our study has a retrospective nature with a small number of cases. Second, we cannot offer the pathologic data to represent the status of Leydig cells or intraprostatic androgen with its target genes at the molecular level. Finally, we cannot clearly explain the heterogeneity in treatment responses of bilateral orchiectomy observed between responders and nonresponders. Nevertheless, our study highlights the clinical effectiveness of surgical castration by bilateral orchiectomy in some CRPC patients who are resistant to initial ADT, and provides the potential mechanisms of these phenomena.

In summary, despite the limited number of patients for statistical analysis, our results shed light again on the clinical benefits of surgical castration by bilateral orchiectomy prior to systemic chemotherapy in some CRPC patients after initial hormone therapy. Further histopathological analysis with large case numbers is required to support our preliminary results.

Conflicts of interest

We certify that there are no conflicts of interest, including specific financial interests, relationships and affiliations relevant to the subject materials described in this manuscript.

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