RESEARCH ARTICLE

Third-line Hormonal Therapy to Treat Prostate Cancer Relapse after Initial and Second-line Hormonal Therapy: Report of 52 Cases and Literature Review

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Abstract

The aim of this study was to evaluate the efficacy of third-line combined androgen blockade (CAB) therapy for castration-resistant prostate cancer that relapsed after primary and second-line CAB. We retrospectively reviewed the medical records of 52 patients who received first-, second-, and third-line CAB therapy (medical or surgical castration, plus steroidal antiandrogen of chlormadinone acetate, or nonsteroidal antiandrogen of flutamide or bicalutamide). For cumulative analysis, we searched the PubMed database and identified a total of 50 cases published in English. Including our cases, this provided a total of 102 cases for analysis. In our study cohort, 11 cases (21.2%) achieved more than 50% reduction of serum prostate-specific antigen (PSA) on initiation of third-line CAB. We found that third-line CAB with nonsteroidal antiandrogen after second-line CAB with steroidal antiandrogen exhibited favorable results, with a positive response in six of 13 patients (46.2%). Cumulative analysis findings were comparable. Regarding the timing of third-line CAB administration, 15 patients had started at a PSA equal to or less than 4.0 ng/ml, and eight of them (53.3%) showed a positive response to treatment, compared to only three of 37 patients (8.1%) whose PSA at the initiation of third-line therapy was higher than 4.0 ng/ml ($p<0.001$). We conclude that third-line CAB with nonsteroidal antiandrogen would be particularly useful for patients whose cancer progressed after second-line CAB with steroidal antiandrogen. The timing of treatment seems to be important because the higher the PSA at the start of third-line therapy, the lower the PSA response rate.

Keywords: prostate cancer - hormonal therapy - alternative antiandrogen - CRPC

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Introduction

Hormonal therapy has a well-defined role in patients who have metastatic prostate cancer and remains a mainstream treatment for their management, and even for localized prostate cancer the use of it has been widespread, especially among older patients (Situmorang et al., 2012). In clinical practice, several therapeutic strategies for hormonal therapy are used, such as an oral antiandrogen, a luteinizing hormone-releasing hormone (LH-RH) agonist, or surgical castration. Oral steroidal antiandrogens such as cyproterone acetate or chlormadinone acetate (CMA), or nonsteroidal antiandrogens such as flutamide (FLT), bicalutamide (BCL) or nilutamide (NIL) are also administered to competitively block testosterone and/or dihydrotestosterone by binding to androgen receptors. Another strategy, known as combined androgen blockade (CAB), which combines an antiandrogen with either chemical or surgical castration, has been widely applied to metastatic disease (Akaza et al., 2009; Labrie, 2010). Unfortunately, in the majority of patients, the benefit of CAB therapy is only temporary.

It is known that some patients with progressive disease who have undergone initial CAB therapy may respond to second-line CAB therapy with alternative antiandrogens (Scher et al., 1997; Joyce et al., 1998; Desai et al., 2001; Kojima et al., 2004; Miyake et al., 2005; Lam et al., 2006; Okihara et al., 2007; Nishimura et al., 2007; Suzuki et al., 2008; Okegawa et al., 2010; Choi et al., 2011) because the latter likely have different functional interactions with the androgen receptor. These previous investigators reported that a more than 50% reduction of prostate-specific antigen (PSA) after second-line CAB therapy was observed in 22-49% of patients. Even patients

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with progressive disease after second-line CAB therapy might respond to third-line treatment. However, the role of alternative antiandrogens as third-line treatment is less clear and the reported response rate has varied according to the number of patients and the antiandrogen sequence of such studies. The response rate to third-line CAB therapy has been reported to be 0-60% (Scher et al., 1997; Desai et al., 2001; Kojima et al., 2004; Okihara et al., 2007; Okegawa et al., 2010).

In the present study, we evaluated 52 patients with prostate cancer that relapsed after primary and second-line CAB therapy, and we assessed the effect of subsequent third-line hormonal therapy. We also reviewed 50 cases of third-line CAB therapy published in the English language literature, and summarized them to identify good candidates who would benefit from this approach.

Materials and Methods

After receiving institutional review board approval, we retrospectively reviewed the medical records of 52 patients who received first-, second- and, third-line CAB therapy (LH-RH agonist, plus 100 mg of CMA, 375 mg of FLT, or 80mg of BCL daily) during the period of 2001-2011 at three institutions. When first- and second-line therapies were judged to have failed, subsequent third-line hormonal therapy was started, but the antiandrogen drug sequence was left to the individual doctor's discretion. In cases of medical castration LH-RH agonist was not discontinued during treatment.

Data assessed included age, PSA level at diagnosis, Gleason score, past history of local therapy, duration of prior hormonal therapy, baseline PSA level at the initiation of third-line therapy, baseline PSA doubling time (DT), type of antiandrogen, and the presence of distant metastasis. Gleason scores were obtained from medical records. Serum PSA determinations were obtained 4 weeks before starting third-line therapy, immediately before (baseline PSA level), and every 4 weeks thereafter. PSA-DT was calculated, assuming first-order kinetics as reported previously (Maffezzini et al., 2007). Baseline PSA-DT at the initiation of third-line therapy was calculated using baseline PSA levels and those obtained 4 weeks prior to starting therapy.

The starting point of this study was the administration of third-line CAB therapy, and the primary end point was a response to therapy. We defined a greater than 50% decrease in PSA compared with baseline as a "response". As the secondary end point, we analyzed cancer-specific survival (CSS) after initiation of third-line CAB therapy. The median follow-up intervals after diagnosis of prostate cancer, after first-line antiandrogen administration, and after third-line antiandrogen administration were 6.2 years (range, 0.8 to 12.1), 5.8 years (range, 0.8 to 12.1), and 2.3 years (range, 0.1 to 8.4), respectively.

To identify published cases of third-line CAB therapy, the PubMed database was searched using the terms "alternative antiandrogen" and "prostate cancer". We also reviewed the reference lists of the identified publications and relevant review articles for additional pertinent studies. We included patients treated with third-line CAB with alternative antiandrogen after second-line CAB in our cumulative analysis.

CSS curves were constructed using the Kaplan-Meier method, and were compared using the log-lank test. The difference in continuous measurements between two groups was analyzed using the Mann-Whitney test. To categorize continuous measurements we used the cut-off point that produced the minimum p value found by testing all possible cut-off points (Mazumdar and Glassman; 2000). All such cut-off points were then rounded up or down to clinically relevant values. The two-sided Fisher exact test was used to determine if there were nonrandom associations between two categorical variables. Statistical significance was determined at $p<0.05$. These analyses were performed with SPSS software, version 20 (SPSS Inc, Chicago, IL, USA).

Results

The characteristics of the 52 patients enrolled in this study are summarized in Table 1. The median age of the patients was 71.9 years (range, 58.0 to 92.3) at the time of diagnosis of prostate cancer, and the median PSA value was 123 ng/ml (range, 2.9 to 4870). The Gleason score was 6 in 4 (7.7%) patients, 7 in 19 (36.5%), 8 in 9 (17.3%), 9 in 16 (30.8%), and 10 in 4 (7.7%) patients. At the initial diagnosis, 12 patients (23.1%) had localized prostate cancer and 11 (21.2%) were locally advanced without metastasis. Eight patients (15.4%) had received local therapy (radical prostatectomy and/or radiation therapy), although all experienced subsequent PSA failure before the induction of hormonal therapy. Fifty of 52 patients (96.2%) responded to first-line CAB initially, and a response to subsequent second-line CAB with alternative antiandrogen was observed in 18 patients

Table 1. Patient Characteristics

Total number of patients		52 patients
Age	at diagnosis	58.0 to 92.3 years (median 71.9 years)
	at 3rd-line therapy	64.4 to 96.1 years (median 76.4 years)
PSA value	at diagnosis	2.9 to 4870 ng/ml (median 123 ng/ml)
	at 3rd-line therapy	0.41 to 455 ng/ml (median 7.7 ng/ml)
Gleason score at diagnosis	≤6	4 (7.7%)
	7	19 (36.5%)
	8	9 (17.3%)
	9	16 (30.8%)
	10	4 (7.7%)
Clinical stage at diagnosis	T2N0M0	12 (23.1%)
	T3N0M0	11 (21.2%)
	N1 and/or M1	29 (55.8%)
Metastasis at diagnosis	yes	29 (55.8%)
	bone	18 (34.6%)
	visceral	24 (46.2%)
	no	23 (44.2%)
Metastasis at 3rd-line therapy	yes	32 (61.5%)
	bone	29 (55.8%)
	visceral	31 (59.6%)
	no	20 (38.5%)
Local therapy	yes	8(15.4%)
	no	44 (84.6%)
Response to 1st-line CAB	yes	50 (96.2%)
	no	2 (3.8%)
Response to 2nd-line CAB	yes	18 (34.6%)
	no	34 (65.4%)
PSA-DT at 3rd-line therapy administration		1.2 to 23.1 months (median 5.3 months)
Duration of prior hormonal therapy		9.8 to 114 months (median 48.0 months)

*PSA; prostate-specific antigen, CAB; combined androgen blockade, DT; doubling time

(34.6%). However, PSA progression ultimately occurred in all patients. The median age of the patients at third-line CAB administration was 76.4 years (range, 64.4 to 96.1). The median baseline PSA value at that time was 7.7 ng/ml (range, 0.41 to 455), and 32 patients (61.5%) had distant metastasis. PSA-DT ranged from 1.2 to 23.1 months (median 5.3), and the median duration of prior hormonal therapy (first- plus second-line CAB) before third-line administration was 48.0 months (range, 9.8 to 114).

Patients received four different sequences of antiandrogens, and Figure 1 shows each PSA response rate after changing the agent from the previous hormonal therapy. Upon initiation of third-line CAB, 11 cases (21.2%) achieved more than a 50% reduction of serum PSA, any reduction in PSA from baseline was observed in 21 patients (40.4%), and the PSA level continued to increase in the remaining 31 (59.6%). Of 11 PSA responders to third-line CAB therapy eight had PSA progression finally, and the median response duration was 9.8 months (range, 3.1 to 23.8). The remaining three cases were still responsive to third-line CAB, and their observation durations were 8.6, 23.3, and 34.0 months, respectively.

A change in antiandrogen from second-line CMA to third-line FLT demonstrated the most favorable response rate of 46.2% (6 of 13 patients). To clarify the clinical differences between third-line responders and non-responders, we compared these groups with respect to several factors (Table 2), and we found that third-line responders tended to have lower baseline serum PSA than non-responders (p=0.001). Eight of 15 patients (53.3%) that had started third-line CAB at a PSA equal to or less than 4.0 ng/ml showed a positive response to treatment. In contrast, only three of 37 patients (8.1%) whose PSA at the initiation of third-line therapy was higher than 4.0 ng/ml responded (p<0.001). We found no significant difference in baseline PSA level between 13 patients treated with FLT after CMA and the other 39 patients (median 6.9 *vs* 10.2 ng/ml, mean 35.3±91.8 *vs* 32.7±73.7 ng/ml, p=0.112).

During the follow-up period, third-line hormonal therapy was discontinued in 47 patients (87.0%). Thereafter, subsequent chemotherapy with oral estramustine phosphate sodium hydrate was conducted in 22 patients (46.8%), and chemotherapy with docetaxel and prednisolone was administered in another eight patients (17.0%). Three patients (6.4%) received oral dexamethasone, and two patients (4.3%) were treated with oral ethinylestradiol. The remaining 12 patients (25.5%) received supportive care only. Finally, during the follow-up periods, 24 patients (46.2%) died due to prostate cancer, and two patients (3.8%) died of other causes. We compared the survival of the third-line responders and non-responders as shown in Figure 2; the CSS curves demonstrated that there was a significant difference between these two groups (p=0.019).

Next, we performed a literature search for reported cases of third-line CAB therapy, and identified a total of 50 cases published in English for review. Including our cases, this provided a total of 102 cases for systematic

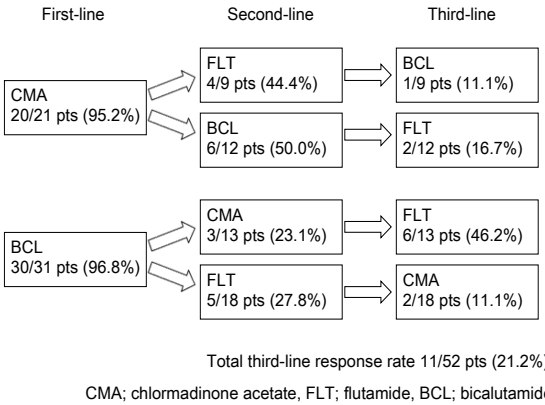

Figure 1. Responders for Alternative Antiandrogen Therapy in the CAB setting, Changing Antiandrogens from First-line to Second-line and from Second-line to Third-line

Table 2. Association between Clinicopathological Factors and Response to Third-Line CAB

	Responders (n=11)	Non-responders (n=41)	p-value
Age (years)			0.148
Median	74.7	76.6	
Mean±SD	74.5±6.0	77.9±7.9	
Duration of prior HT (months)			0.695
Median	55.3	43.6	
Mean±SD	46.2±24.2	45.5±28.9	
Baseline PSA value (ng/ml)			0.001
Median	1.3	10.6	
Mean±SD	4.8±7.8	41±86	
PSA-DT (months)			0.779
Median	5.1	5.8	
Mean±SD	6.0±3.5	7.9±6.5	
Gleason score			0.182
6, 7	7	16	
8, 9, 10	4	25	
Metastasis			0.081
No	7	13	
Yes	4	28	
Response to 2nd-line CAB			>0.999
Yes	4	14	
No	7	27	
Order of antiandrogens			0.019
BCL→CMA→FLT	6	7	
The others	5	34	

*CAB; combined androgen blockade, SD; standard deviation, HT; hormonal therapy, PSA; prostate-specific antigen, DT; doubling time, BCL; bicalutamide, CMA; Chlormadinone acetate, FLT; flutamide

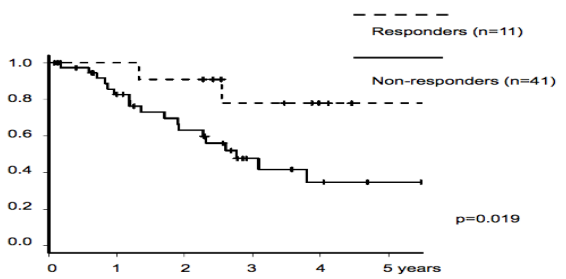

Figure 2. Difference in Subsequent Cancer-Specific Survival Rates between 11 Responders and 41 Non-Responders to Third-line CAB. The time point zero was the initiation of third-line hormonal therapy

Table 3. Summary of Number of Patients Who Responded to Third-Line CAB

	3rd-line CAB with nonsteroidal AA after steroidal AA		3rd-line CAB with steroidal AA after nonsteroidal AA		3rd-line CAB with nonsteroidal AA after nonsteroidal AA		
	CMA→FLT	CMA→BCL	FLT→CMA	BCL→CMA	FLT→BCL	BCL→FLT	FLT/BCL→NIL
Urology (Desai et al., 2001)							2/4
J Urol (Kojima et al., 2004)		2/3			0/4	3/10	
Int J Urol (Okihara et al., 2007)	0/1	1/3	0/6	0/1	1/3	0/1	
Int J Urol (Okegawa et al., 2010)	0/3	1/2	0/6	0/5	0/2	2/6	
Our study	6/13		2/18		1/9	2/12	
Total	6/17 (35.3%)	4/8 (50.0%)	2/30 (6.7%)	0/6 (0.0%)	2/18 (11.1%)	7/29 (30.6%)	2/4 (50.0%)
	10/25 (40.0%)		2/36 (5.6%)		11/51(21.6%)		

*CAB; combined androgen blockade, AA; antiandrogen, Chlormadinone acetate (CMA) was used as steroidal antiandrogen, and flutamide (FLT), Bicalutamide (BCL), or nilutamide (NIL) were administered as nonsterodal antiandrogens

analysis, all of which had been treated with second- and third-line CAB, using steroidal antiandrogen (CMA), or three types of nonsteroidal antiandrogens (FLT, BCL, or NIL). As described in Table 3, changing from a second-line steroidal antiandrogen drug to a third-line nonsteroidal was effective in 10 of 25 patients (40.0%). Meanwhile, the response rate to third-line CAB with steroidal antiandrogen after nonsteroidal treatment was only 5.6% (two of 36 patients).

Discussion

Most patients with advanced prostate cancer eventually experience relapse after primary CAB therapy, and secondary hormonal therapy is a typical treatment strategy when this occurs. Second-line CAB therapy with an alternative antiandrogen has been reported to be effective in some patients (Scher et al., 1997; Joyce et al., 1998; Desai et al., 2001; Kojima et al., 2004; Miyake et al., 2005; Lam et al., 2006; Okihara et al., 2007; Nishimura et al., 2007; Suzuki et al., 2008; Okegawa et al., 2010; Choi et al., 2011), and is now a treatment option as advocated in clinical guidelines in American Urological Association (2013), European Association of Urology (2013), and National Comprehensive Cancer Network (2014). However, in the majority of cases the disease becomes resistant to second-line CAB. Thereafter, third-line CAB may sometimes be administered, reserving systemic chemotherapy with toxicity for later, although the efficiency of third-line CAB therapy has not been sufficiently evaluated.

A few small studies have evaluated the activity of third-line CAB, and the reported response rates varied due to the limited number of patients and heterogeneous populations. Scher et al. (1997) reported that none of 12 patients who had received two or more prior hormone treatments responded to CAB with 200 mg of BCL. However, they did not report information on prior therapies, and therefore we did not include their data in our cumulative analysis. Desai et al. (2001) found that three of five patients (60.0%) who received third-line NIL (150 or 300 mg) after prior FLT and BCL achieved a greater than 50% decrease in PSA, although we had to exclude one of these cases from our cumulative analysis because antiandrogens were not administered in the CAB setting. Kojima et al. (2004) reported a response rate of 29.4% (five of 17 patients) with third-line CAB with nonsteroidal antiandrogens. Meanwhile, another two studies including patients with third-line CAB with steroidal antiandrogen (CMA) demonstrated lower response rates of 13.3% and 12.5%, respectively (Okihara et al., 2007; Okegawa et al., 2010). These results were included in our cumulative analysis.

A previous collaborative meta-analysis of 27 randomized trials examined the effects of the different antiandrogens, and found that nonsteroidal antiandrogens (NIL and FLT) were superior to steroidal antiandrogen (cyproterone acetate) in the CAB setting (Prostate Cancer Trialists' Collaborative Group, 2000). Likewise, in our study we found that third-line CAB with FLT after CMA exhibited favorable results, with a positive response in six of 13 patients (46.2%). Our cumulative analysis also demonstrated that third-line CAB with nonsteroidal antiandrogen after steroidal antiandrogen was effective in 10 of 25 patients (40.0%). Conversely, the response rate to third-line CAB with steroidal antiandrogen after nonsteroidal antiandrogen was limited (two of 36 patients, 5.6%). We also found that more than half of the cases (eight of 15 patients) that had started third-line therapy at a PSA equal to or less than 4.0 ng/ml showed a positive PSA response. In contrast, the proportion of PSA responders dwindled as the PSA at the start of third-line therapy increased. A similar tendency in terms of the correlation between low PSA level and good response was observed in previous reports on second-line therapy (Suzuki et al., 2008; Okegawa et al., 2010). These findings suggest that alternative antiandrogen therapy could be expected to have a favorable effect in patients with prostate cancer with comparatively indolent characteristics and limited disease extent. Furthermore, our data suggest that survival in responders to third-line therapy was significantly better than survival in non-responders, which again was compatible with previous results on second-line CAB (Suzuki et al., 2008; Okegawa et al., 2010).

The current study analyzed retrospective data obtained in a chart review of medical records, and there are thus significant limitations. There may be clinical bias in terms of those who received third-line CAB therapy and those who did not. It was not clear from this single-arm study whether third-line CAB therapy could provide survival benefit compared to other therapeutic options for CRPC patients, and risk of long-term hormonal treatment-related complications also should be considered (McGrowder, 2012). Since the number of eligible patients was small,

it was impossible to perform multivariate analysis in order to detect factors associated with a PSA response to third-line CAB therapy. The small number of patients also made it difficult to set various cut-off points of continuous measurements of PSA. Therefore, in order to reach definite conclusions concerning the clinical usefulness of third-line CAB, further investigations will be required.

In conclusion, we conclude that third-line CAB therapy was effective to some degree in patients with castration-resistant prostate cancer who had already received primary and second-line CAB therapy. Third-line CAB with nonsteroidal antiandrogens was particularly useful for patients whose cancer had progressed after second-line CAB with steroidal antiandrogens, and should be considered before embarking on the next therapuic manoeuvre. The timing of treatment seems to be important because the higher the PSA at the start of third-line therapy, the lower the PSA response rate.

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