Secondary Hormonal Therapy in Men With Castration-Resistant Prostate Cancer

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Abstract

A retrospective cohort of 436 men with CRPC was used to evaluate the profile of secondary hormonal therapy response in CRPC. Longer duration of primary androgen deprivation therapy was associated with longer duration of secondary hormonal therapy. Men who received the first secondary hormonal treatment for longer than 6 months were more likely to respond to subsequent secondary hormonal therapies.

Background: Androgen receptor (AR) signaling remains important in castration-resistant prostate cancer (CRPC) and sequential responses to hormonal therapies are observed. Little is known about the factors associated with responsiveness to secondary hormone therapy (HT). **Methods:** We retrospectively identified patients with CRPC who were treated with secondary HT. Patient characteristics and types and duration of secondary HT were analyzed. Selected clinical characteristics and their association with duration of secondary HT were evaluated. **Results:** Of 436 eligible patients, 321 (74%) and 87 (20%) received at least two or four secondary HT regimens, respectively. Median duration of time on primary androgen deprivation therapy alone (ADT) and secondary HT were 24.0 months (range, 1.5 to 171.8 months) and 30.3 months (range, 0.6 to 156.1+ months), respectively. Patients who received primary ADT $\geq$ 24 months received secondary HT for a median duration of 40.0 months, whereas men who received ADT $<$ 24 months had a median duration of 18.4 months on secondary HT ($P < .0001$). Metastatic disease at secondary HT initiation was associated with a shorter time on secondary HT ($P = .0001$). Patients who received the first secondary HT for $\geq$ 6 months were more likely to have a longer duration on subsequent secondary HT compared with the men who received the first secondary HT $<$ 6 months ($P = .0001$). **Conclusions:** Treatment durations of secondary HT are variable. Longer duration of primary ADT was associated with longer duration of secondary HT. These results imply that AR signaling remains an important therapeutic target in CRPC.

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Introduction

Since the seminal work of Huggins and Hodges, androgen deprivation therapy (ADT) has been the mainstay of systemic therapy for hormone-sensitive prostate cancer (HSPC).[1] Initiation of ADT results in clinically significant responses in established disease and declines of prostate-specific antigen (PSA) levels in most patients. The duration of response to primary ADT is variable, ranging from months to years. Despite initial favorable responses, most patients ultimately progress to castration-resistant prostate cancer (CRPC), usually characterized initially by an increasing PSA level followed by progression of radiographically detected metastases.

The androgen receptor (AR) pathway is essential for the development and progression of prostate cancer. In CRPC, despite castrate levels of serum testosterone, AR remains active and regulates the transcription of genes involved in cell growth including PSA. Alterations in AR signaling involved in CRPC are not fully understood. However, multiple adaptive mechanisms favoring growth in a low-androgen environment may be involved, including *AR* gene ampli-

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fication, *AR* mutation resulting in activation by weak androgens and nonphysiologic ligands, constitutively active *AR* splice variants, increased AR protein, altered balance between AR coactivators and co-repressors, and intratumoral androgen synthesis from the intracrine synthesis of androgens.[2-10]

Secondary hormonal therapies (HTs) are commonly used in the management of CRPC because of its mild toxicity profile and ease of administration. The efficacy of secondary HT in some patients with CRPC shows the continued importance of AR signaling in CRPC. However, little data is available with regard to the natural history of CRPC and clinical predictors of response to secondary HT. It is common in our practice for some patients to respond well to a series of secondary HTs while others do not respond to any. In previously published retrospective analyses of nilutamide and ketoconazole in CRPC, we found that responders to secondary HT were likely to have had a longer duration of time on primary ADT compared with non-responders.[11,12] We hypothesized that there may be an association between responsiveness to primary ADT and subsequent response to secondary HT. We present data from our institutional prostate cancer database describing the natural history of CRPC before initiation of chemotherapy and factors associated with responsiveness to secondary HTs.

Patients and Methods

Database

The cohort analyzed was generated from the Prostate Clinical Research Information System (CRIS) at Dana-Farber Cancer Institute (DFCI).[13] This protocol was approved by the Institutional Review Board at the Dana-Farber/Harvard Cancer Center. Data are stored in an Oracle relational database (Oracle, Redwood Shores, CA). Data are entered from multiple sources, including medical records (including non-DFCI medical records if available), institutional laboratory results (including outside PSA results if available), patient registration, pharmacy information, and clinician forms. Quality control is performed on a regular basis to ensure Prostate CRIS accuracy and completeness. All patients seen at DFCI and Brigham and Women's Hospital with a diagnosis of prostate cancer are approached to participate in the database. The overall consent rate for participation in the database is 88%. At the time of analysis, approximately 6200 men had consented to provide clinical data into Prostate CRIS. The current version of Prostate CRIS became available for prospective data entry in November 2001.

Patient Selection and Quality Control

We identified 471 patients who had been treated with secondary HT for CRPC. Those men were identified by running a Business Object (Business Object, Inc., San Jose, CA) report for any patients in Prostate CRIS whose treatment status is/was "receiving secondary hormonal therapy" and whose disease status is/was "non-metastatic/metastatic, castration resistant prostate cancer." Secondary HT agents included anti-androgens (bicalutamide, nilutamide, and hydroxyflutamide), adrenal androgen/CYP17 lyase inhibitors (ketoconazole, aminoglutethimide, steroids), and estrogens (diethylsilbesterol, premarin, PC-SPES). A total of 35 patients were excluded from the analysis cohort because of indeterminate starting dates of either primary ADT or secondary HT (N = 19), a history of chemotherapy for CRPC before initiating secondary HT (N = 10), significant lack of follow-up data (N = 4), or no documentation of secondary HT because of database error (N = 2). As a quality-control measure, a research physician (MN) trained in genitourinary oncology reviewed the primary medical records of a subset of 204 patients: 49 (~10% of cohort) were systematically reviewed across 10 variables; 155 had a focused review of start dates of ADT and secondary HT, use of combined ADT with an anti-androgen as primary HT, and use of chemotherapy before ADT.

Terminology

Because the proper terminology for hormonal therapies beyond "primary" has not been well-established, we use the terminology "first," "second," third," etc, secondary HT for additional courses of hormonal therapy regimens for CRPC.

Statistical Analysis

Patient and disease characteristics are summarized as numbers and percentages for categorical variables and median and range for continuous variables. Duration of primary ADT was defined as the time between the date of first luteinizing hormone-releasing hormone (LHRH) agonist/antagonist or orchiectomy and the start date of first secondary HT. We defined the date of first shot of LHRH agonist/antagonist or date of orchiectomy as start date of primary ADT when it was given for increasing PSA levels and/or metastatic disease. Neoadjuvant and adjuvant ADT were not included in the duration of primary ADT. Duration of secondary HT was defined as time between the start date of first secondary HT regimen and the start date of first chemotherapy for CRPC for patients receiving chemotherapy, or was censored at the end of the last secondary HT regimen or the last known PSA or imaging dates. Duration of secondary HT refers to all lines of secondary HT. Distribution of duration of secondary HT was estimated using the Kaplan-Meier method. Associations between duration of secondary HT and patient disease characteristics were assessed using log rank tests. Duration of each secondary HT regimen was defined as the time between the start date and the end date of the regimen. For patients who were still on a secondary HT regimen at the time of analysis, duration of the regimen was censored on the last known PSA or imaging date. The statistical analysis was performed using SAS v.9 (SAS institute Inc, Cary, NC) and $P < .05$ (two-sided) was considered to be statistically significant.

Results

Patients and Disease Characteristics

The final cohort included 436 patients treated with secondary HT that had been initiated between May 1993 and September 2008 (Table 1). Median follow-up since secondary HT initiation was 69.4 months (range, 1.6 to 180.5 months). Median age at the start of the first secondary HT was 69 years (interquartile: 62, 75). Median PSA at the first secondary HT was 6.8 ng/mL (interquartile: 1.8, 23). A total of 298 patients (68%) had metastatic disease at secondary HT initiation, with the remainder treated for an increasing PSA level alone. Median PSA levels at first secondary HT in men with and without metastatic disease was 8.77 ng/mL (interquartile: 2.58, 32) and 3.88 ng/mL (interquartile: 1.15, 8.55), respectively.

Table 1 Patient and Disease Characteristics of 436 Patients With Castration-resistant Prostate Cancer Who Received Secondary Hormonal Therapy

	Median	Interquartile Range
At Diagnosis		
Age, years (N = 413)	62	56-68
PSA (N = 360)	16	7.25-56.6
	N	**%**
Biopsy Gleason Score		
<6	65	15
7	139	32
> 8	161	37
Unknown	71	16
Clinical T Stage		
T1	141	32
T2	111	25
T3-4	23	5
Unknown	161	37
Type of Local Therapy		
RP	107	25
RT	141	32
RP+RT	42	10
None	116	27
Unknown	29	7
Hormonal Therapy as Part of Local Therapy		
Yes	103	24
No	333	76
At ADT Initiation		
Metastatic Disease		
Yes	234	54
No	202	46
Type of ADT		
LHRH monotherapy or Orchiectomy	264	61
Combined ADT	172	39
PSA (ng/mL)		
≤ 4	57	13
> 4 – 10	51	12
> 10 - 20	55	13
> 20	156	36
Unknown	116	27
At Secondary Hormonal Therapy		
	Median	**Interquartile Range**
Age, Years	69	62-75
	N	**%**
Metastases		
Yes	298	68
No	138	32
PSA (ng/mL)		
≤ 4	131	30
> 4 – 10	84	19
> 10 – 20	48	11
> 20	96	22
Unknown	77	18

Abbreviations: ADT = androgen deprivation therapy; LHRH = luteinizing hormone releasing hormone; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

Secondary HT Administration

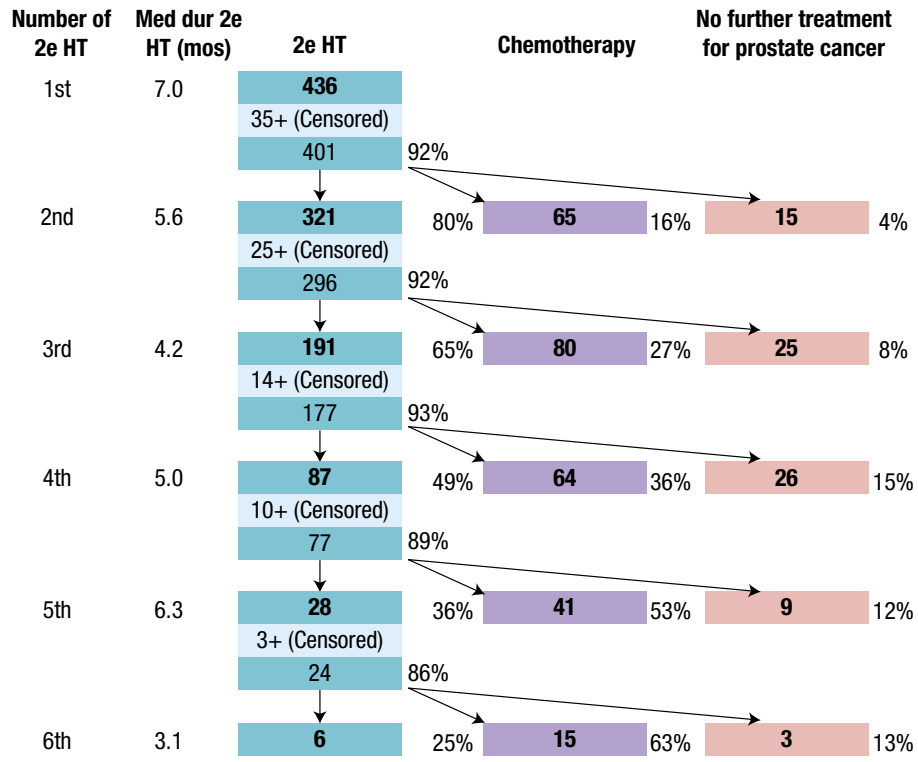
At the time of analysis, 35 patients (8%) were still on their first regimen of secondary HT. A total of 321 patients (74%) received at least two secondary HT regimens. A total of 191 patients (44%) received three or more regimens, and 87 men (20%) received more than four. Twenty-seven patients (6%) received five or six regimens. Figure 1 represents the percentages of patients who received the each course of secondary HT, those who received chemotherapy after failing secondary HT, and those who did not receive further treatment for prostate cancer.

Median duration of time on secondary HT was 30.3 months (range, 0.6 to 156.1+ months). After cessation of the first secondary HT, 65 men (16%) received chemotherapy. Of 296 men who stopped their second secondary HT, 191 men (65%) received a third-line secondary HT and 80 (27%) received chemotherapy. Of 177 patients who stopped their third-line secondary HT, 87 (49%) received a fourth-line secondary HT, and 64 (36%) received chemotherapy. Of 77 men who stopped a fourth-line secondary HT, 28 men (36%) received a fifth-line secondary HT and 41 men (53%) received chemotherapy (Figure 1).

Duration of Each Secondary HT Regimen and Type of Agents Used

Figure 2 depicts the distribution and median duration on treatment for each secondary HT category. As first-line secondary HT, anti-androgens were most commonly used (70%) followed by adrenal androgen/CYP17 lyase inhibitors (20%). The majority (66/87; 76%) of patients who received adrenal androgen inhibitors as the first secondary HT had already received an anti-androgen as part of primary combined ADT. Adrenal androgen/CYP17 lyase inhibitors (42%) and anti-androgens (39%) were almost equally used as second-line secondary HT. There was a pattern that increasing numbers of patients received estrogens as they received further lines of secondary HT. More patients received "other" secondary HT regimens after receiving two secondary HT regimens, suggesting that more patients were likely to participate in clinical trials after receiving several secondary HT regimens.

Figure 1 Treatment Patterns of a Cohort of 436 Men With Castration-resistant Prostate Cancer With a Median Follow-up of 69.4 Months Since Initiation of the First Secondary Hormone Therapy



Association Between Primary ADT and Duration of Secondary HT

Median duration of time on primary ADT was 24.0 months (range, 1.5 to 171.8 months). Because all patients in this cohort progressed on ADT, we dichotomized duration of ADT at the median of 24 months and observed the association between duration of primary ADT and duration of secondary HT. Patients who received primary ADT ≥ 24 months received secondary HT for a median duration of 40.0 months (range, 0.6 to 156.1+ months), whereas men who were on primary ADT < 24 months had a median duration of 18.4 months (range, 0.7 to 119.5 months) on secondary HT ($P < .0001$).(Table 2; Figure 3)

A total of 234 patients (54%) had metastatic disease (M+) at primary ADT initiation. Median duration of time on secondary HT was shorter in M+ patients when compared with those without metastases (M-) (21.6 months versus 36.7 months; $P = .0013$).

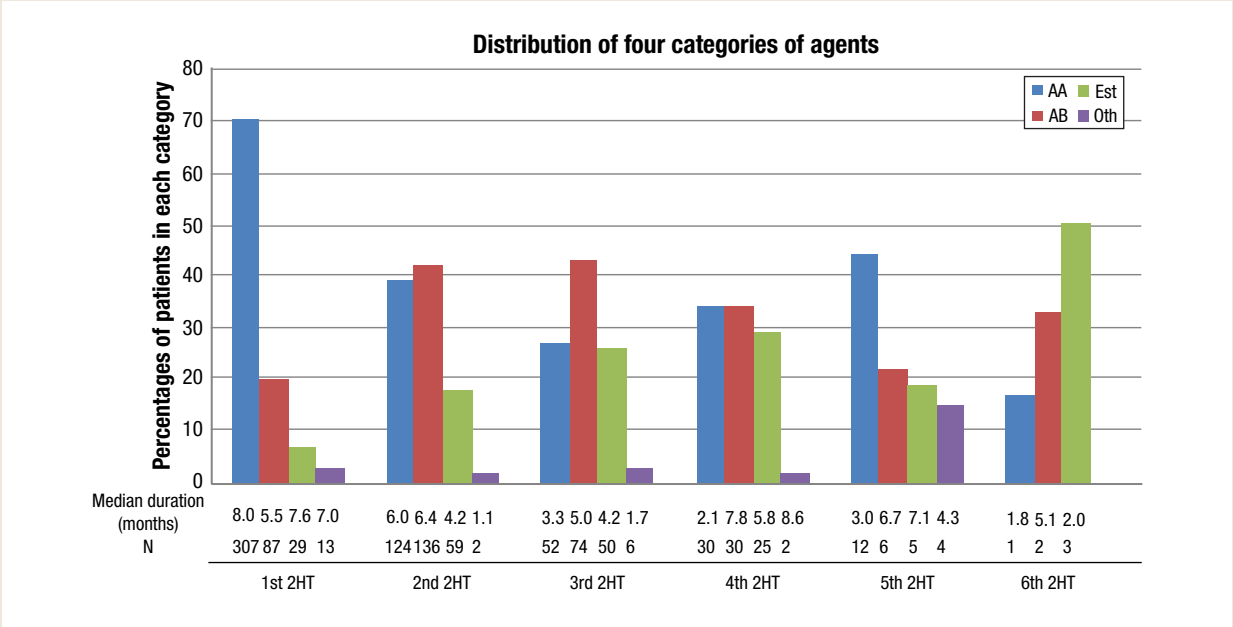
Furthermore, we looked for associations among patients based on metastatic status at primary ADT initiation, duration of primary ADT, and duration of secondary HT. Median durations of secondary HT were 38.5, 33.6, 47.0, and 14.8 months in M− patients with primary ADT ≥ 24 months, M− patients with primary ADT < 24 months, M+ patients with primary ADT ≥ 24 months, and M+ patients with primary ADT < 24 months, respectively. Thus, M+ patients at primary ADT initiation who received primary ADT < 24 months had the shortest duration of secondary HT ($P < .0001$; Table 2). Durations of secondary HT could be long despite the presence of metastases at primary ADT initiation if the responsiveness to primary ADT was greater than the median (24 months).

Association of Metastatic Disease and PSA at Initiation of Secondary HT With Duration of Secondary HT

A total of 298 patients (68%) had metastatic disease at secondary HT initiation. Median duration of secondary HT was shorter in M+ group at secondaryt HT initiation than in the M− group (21.9 and 44.2 months, respectively; $P = .0001$).

We evaluated how PSA levels and metastatic status at secondary HT initiation were associated with duration of secondary HT. PSA levels at secondary HT initiation were significantly associated with duration of secondary HT ($P < .0001$). In addition, we observed a borderline interaction between PSA and metastatic disease ($P = .06$). Patients without metastases at secondary HT initiation had a longer duration of secondary HT regardless of the PSA level (> 10 ng/mL or ≤ 10 ng/mL) compared with M+ patients at secondary HT initiation, with the shortest median duration of secondary HT in M+ patients whose PSA level was > 10 ng/mL at the start of secondary HT (14.9 months).

Figure 2 Distribution of Four Categories of Agents According to the Sequence of Secondary Hormonal Therapy and Median Duration of Treatment Given. Each Regimen of Secondary Hormonal Therapy Was Categorized Into Four Groups: Antiandrogens (AA) Including Bicalutamide, Nilutamide, and Flutamide; Adrenal Androgen Blockers (AB) Including Ketoconazole With or Without Hydrocortisone and Aminogluthethimide; Estrogens (Est); and Others (Oth) Including Investigational Drugs



Duration of the First-line and Subsequent Secondary HT

A total of 321 patients (74%) received at least two or more regimens of secondary HT. We dichotomized the duration of the first-line secondary HT at 6 months for the 321 patients. The duration of the first regimen was associated with the duration of subsequent secondary HT. Median duration of all subsequent secondary HTs after the first regimen was 16.9 months longer in patients who received the first regimen for $\geq$ 6 months compared with those who received the first regimen for $<$ 6 months ($P < .0001$; Figure 4).

Discussion

Secondary HTs are commonly used in the management of CRPC because they often result in clinical responses with acceptable toxicity.[11,12,14-21] The CYP17 lyase inhibitor, abiraterone, recently showed a survival advantage compared to placebo in CRPC patients who were previously treated with chemotherapy, thus changing the paradigm of treatment in CRPC.[22] This exciting result confirms that sequential therapies directed at AR inhibition can have meaningful clinical results. As more effective hormonal agents become available for treating prostate cancer, patient selection and thoughtful sequencing of agents is paramount. Published data describing the natural history of CRPC in patients treated with secondary HTs is lacking and led us to analyze and present these data.[23,24] Although studies have shown that clinical parameters (such as PSA level at baseline, lactate dehydrogenase, alkaline phosphatase, hemoglobin, and performance status) as prognostic factors of survival in men with metastatic CRPC,[25-29] no large study to date has investigated clinical predictors of response to secondary HTs. To that end, we have characterized 436 CRPC patients who were treated with secondary HTs.

A significant observation in our analysis was that the median total duration on secondary HT was longer than the median duration on primary ADT alone, 30.3 versus 24 months, respectively, in this cohort. This result counters to the prevailing notion that the primary clinical response is to initial ADT and that secondary HTs are associated with limited response durations. In fact, many practitioners do not consider treatment with sequential secondary HTs because of the lack of clear treatment guidelines. Most patients in our cohort (74%) received at least two secondary HT regimens and 20% of patients received at least four secondary HT regimens before starting chemotherapy. This data suggests that ongoing responsiveness to AR-directed therapies, including compounds which directly inhibit AR, reduce AR ligand(s) or combination of ligand-receptor approaches.

In this cohort, duration of time on primary ADT was significantly associated with the duration of treatment using secondary HT. Additionally, metastatic disease continued to be associated with response to secondary HT in CRPC; we reported that metastases was associated with response to primary ADT in 553 patients with HSPC.[30] Interestingly, having metastatic disease at ADT initiation did not necessarily mean that patients were unlikely to be responsive to secondary HT. However, having both metastatic disease at ADT initiation and shorter duration of primary ADT ($<$ 2 years) was associated with shorter duration of secondary HT (median duration of secondary HT, 14.8 months). Those patients (metastatic disease at ADT initiation and duration of primary ADT $<$ 2 years) may be

Table 2 Association of ADT History and Disease Characteristics at Start of Secondary Hormonal Therapy With Duration of Secondary Hormonal Therapy

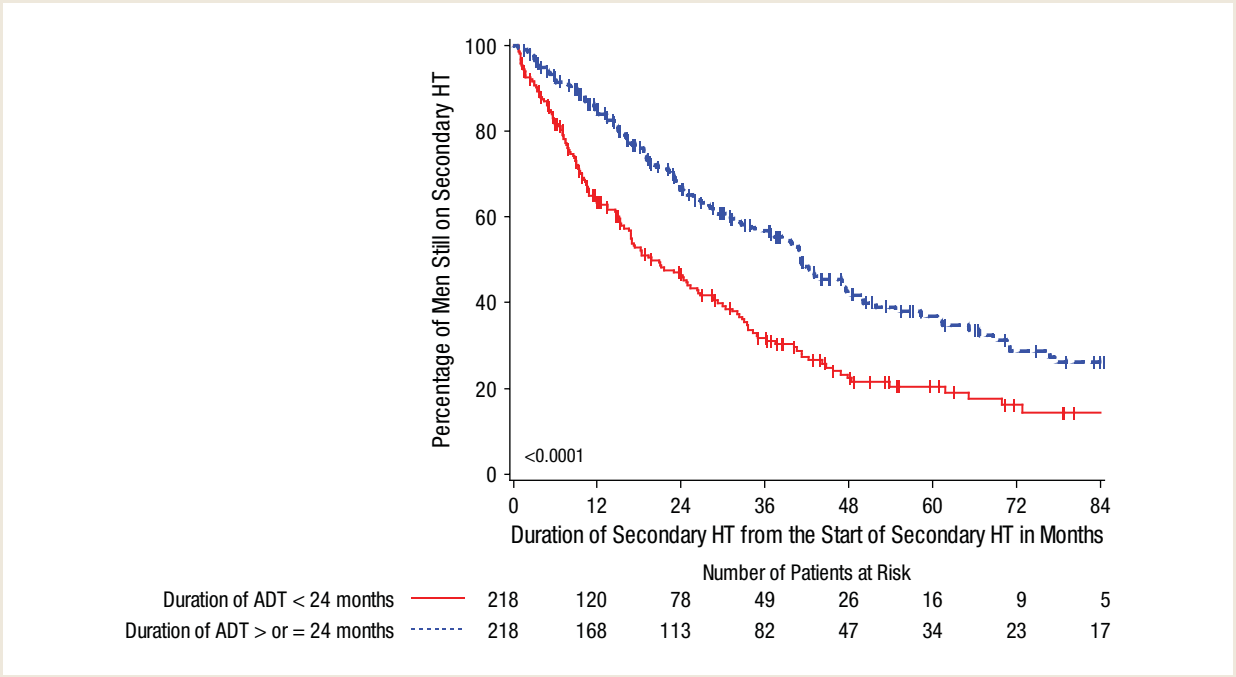
	Patients	Events	Median Duration of Secondary HT (Months)	Log Rank *P* Value
All Patients	436	171	30.3	—
Duration of Primary ADT				<.0001
<24 months	218	150	18.4	
≥ 24 months	218	121	40.0	
Metastases Status at ADT Initiation				.0013
M-	202	118	36.7	
M+	234	153	21.6	
Metastases and Duration of Primary ADT				<.0001
M-, primary ADT ≥ 24 mo	121	69	38.5	
M-, primary ADT <24 mo	81	49	33.6	
M+, primary ADT ≥ 24 mo	97	52	47.0	
M+, primary ADT <24 mo	137	101	14.8	
PSA at ADT Initiation				.43
<10 ng/mL	109	64	29.3	
≥ 10 ng/mL	211	137	28.6	
Metastases Status at Secondary HT Initiation				.0001
M-	138	71	44.2	
M+	298	200	21.9	
Metastases at the Initiation of Secondary HT and Duration of Primary ADT				<.0001
M-, primary ADT ≥ 24 mo	81	39	47.8	
M-, primary ADT <24 mo	57	32	42.2	
M+, primary ADT ≥ 24 mo	137	82	38.5	
M+, primary ADT <24 mo	161	118	14.8	
PSA at Secondary HT Initiation				<.0001
<10 ng/mL	215	120	40.9	
≥ 10 ng/mL	144	111	16.8	
Metastases and PSA at Secondary HT Initiation				
M-, PSA <10 ng/mL	82	46	43.1	<.0001
M-, PSA ≥ 10 ng/mL	22	13	40.9	
M+, PSA <10 ng/mL	133	74	33.1	
M+, PSA ≥ 10 ng/mL	122	98	14.9	

Abbreviations: ADT = androgen deprivation therapy; HT = hormonal therapy; M = metastases; PSA = prostate-specific antigen.

good candidates for combination hormonal therapy, chemotherapy, or clinical trials because the median duration of secondary HT in this population was considerably short compared with others. Of note, the current cohort did not include patients who received chemotherapy for their rapidly progressive disease without receiving secondary HT. Patients with the shortest median duration of secondary HT may be candidates for early chemotherapy for CRPC.

The strong association between duration of primary ADT and duration of secondary HT was consistent with the results from our previous retrospective study of ketoconazole in CRPC. In the ketoconazole study, there was a significant association between response to ketoconazole and duration of primary ADT as well as total duration of all previous hormonal treatments.[11] Although not statistically significant, a similar trend was observed in our nilutamide study.[12] It is noteworthy that men who received the first secondary HT for longer than 6 months were more likely to have prolonged treatment duration of subsequent secondary HT regimens compared to those who received it for less than 6 months. The difference in median duration of subsequent secondary HT was approximately 17 months between the groups (28 versus 11 months). This finding suggests that the AR signaling pathway is more sensitive to suppression with available agents for

Figure 3 Kaplan-Meier Estimates of Duration of Secondary Hormonal Therapy, According to Duration of Primary Androgen Deprivation Therapy



some prostate cancers but not others. Although sequential responses to multiple secondary HT regimens indicate the ongoing importance of the AR pathway, multiple additional growth pathways are also likely involved in prostate cancer survival and resistance to castration. Our findings support the hypothesis that prostate cancer cells develop adaptive mechanisms to changes in the cellular environment created by hormonal manipulations in order to continue using the AR; and sequential inhibition of AR or ligand reduction may result in serial clinical responses and disease stabilization.[31]

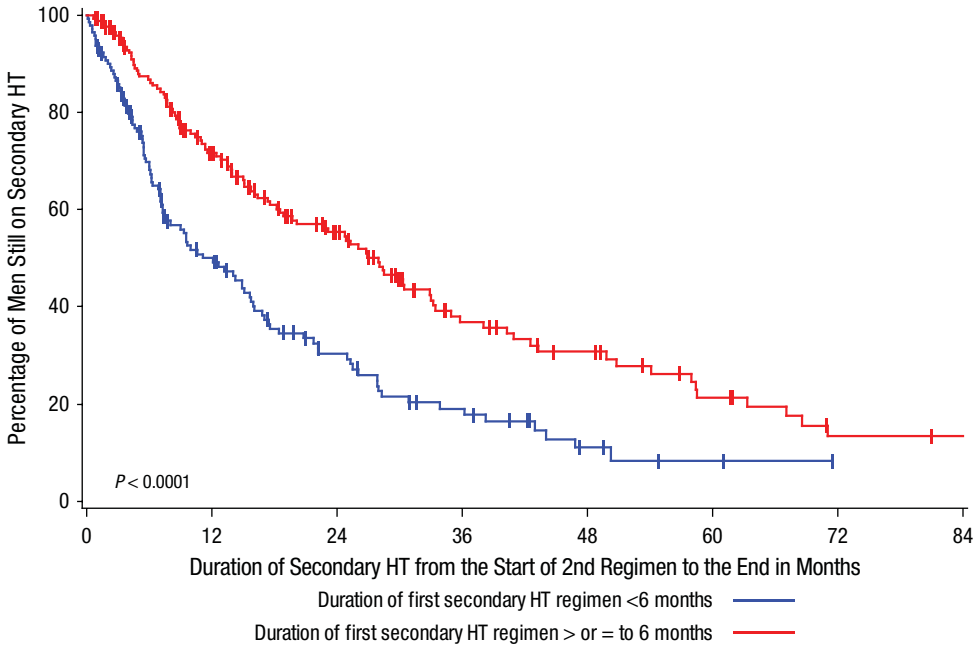
We previously found that genetic variation in the androgen synthesis and metabolism pathway was associated with time to disease progression (TTP) on ADT.[32] Measurement of single nucleotide polymorphisms of genes involved in androgen synthesis and metabolism in the present cohort is ongoing and will be reported separately. In a retrospective report of ketoconazole, previous use of estrogen was associated with a shorter TTP on ketoconazole given in the post-taxane chemotherapy setting.[33] In the present study, although not statistically significant, the median duration of secondary HT was slightly shorter (3 months) in patients with a prior use of ADT as part of local therapy compared to those without (data not shown). It is possible that remote exposure to ADTs allows time for selection of tumor clones with established resistance to subsequent androgen depletion therapies.

The variable responsiveness to secondary HT in men with CRPC creates a compelling need to strategize for personalized therapy based on the clinical and/or molecular features of each patient/tumor. The demonstration of a survival benefit with abiraterone in post-chemotherapy CRPC heralds a new era of prostate cancer HT. Development of additional new secondary HT agents is rapidly evolving.[31,34-37] The mechanisms of action of these new agents include reduction of AR signaling by AR inhibition, AR degradation and inhibition of AR translocation into the cell nucleus (MDV3100, TOK001, ARN-509 (NCT01171898), and reduction of AR ligand through CYP17 inhibition (abiraterone acetate, TOK001, TAK700).[36-39] Whether the CYP17 lyase inhibitors can inhibit tumor intracellular androgen synthesis in addition to inhibition of serum androgens is under investigation. Both abiraterone acetate and MDV3100 have shown responses in taxane-treated patients, suggesting more potent inhibition of AR signaling compared to currently available agents.[33,40]

Along with the development of new drugs, new regimens combining existing and new hormonal agents are being tested.[21,41] The goal of combined regimens is to achieve the maximum response by blocking multiple targets in AR signaling and the interconnected pathways.[21] Because none of the single-agent secondary HT regimens to date have shown consistent and sustained activity, a multitargeted approach may lead to more prolonged responses.

One may argue that our metric of "duration of treatment" (rather than TTP) may not reflect the actual "response" duration to the treatment. However, we believe that it is appropriate to use treatment duration (rather than response duration) as the determinate for stopping a particular therapy based on the physician's clinical judgment of patient benefit. Furthermore, median duration of ADT (24 months) in this cohort is similar to the median TTP on ADT (23.7 months) in our cohort of 553 men with HSPC.[30] In the previous study, we reported that significant predictors of TTP on ADT were metastatic disease at ADT initiation, prior use of ADT as part of local treatment, PSA level at ADT initiation, and Gleason score.[30] In the

Figure 4 Kaplan-Meier Estimates of Duration of Time That Patients Were Treated With Subsequent Secondary Hormonal Regimens After the First Secondary Hormonal Therapy, According to Duration of the First Secondary Hormonal Therapy



	Duration of first 2ºHT	N	Events	Median Duration of subsequent 2ºHT
----------	< 6 months	143	102	11.1 months
----------	≥ 6 months	178	104	28.0 months

present cohort of 436 men with CRPC, none of these predictors except metastatic disease at ADT initiation was significantly associated with duration of secondary HT (data not shown). Despite extensive quality control and rigorous data collection, our study is limited by its retrospective design using a longitudinal database. However, the heterogeneity of our cohort represents "real-world" patients with CRPC treated at an academic center. We anticipate that this data will help physicians counsel patients on the potential efficacy of secondary HT and will assist in the design of clinical trials in CRPC.

In summary, this is the largest cohort (436 men) describing the natural history of CRPC and clinical predictors of responsiveness to secondary HTs. Responses to secondary HT are common and can be prolonged. Duration of time on primary ADT had a significant association with duration of secondary HT. Having metastatic disease at secondary HT initiation was not necessarily a poor predictive factor if the duration of primary ADT was longer than 2 years. Men who had a good response to the first secondary HT were likely to respond to subsequent HTs. Discovering new molecular mechanisms involved in the progression of CRPC will aid in the development of androgen pathway inhibitors. AR-directed therapies will continue to be used in a combined or sequential fashion to abrogate or delay the development of castration resistance. Our findings support the hypothesis that AR signaling remains a vital therapeutic target in CRPC.

Clinical Practice Points

- Despite the common use of secondary hormonal therapies (HTs) in the management of castration-resistant prostate cancer (CRPC), little published data is available that describes the natural history of CRPC and clinical predictors of response to secondary HT.
- The recent demonstration of a survival benefit for the CPY17 lyase inhibitor, abiraterone, in post-chemotherapy CRPC patients heralds a new era in the management of CRPC. The data presented here is the largest cohort describing the natural history of CRPC.
- We now know that CRPC cells maintain androgen receptor signaling through selection of both ligand and receptor changes that favor growth.
- These observations together with the development of multiple new hormonal agents mandate an improved understanding of responses to secondary HT.
- Our data showed that longer duration of time on primary ADT was significantly associated with longer duration of time on secondary HT.

- Patients who continued on the first secondary HT for longer than 6 months were more likely to respond to subsequent secondary HT.
- Although retrospective, our cohort represents the clinical experience of patients treated at a tertiary cancer center.
- The findings can be used to counsel patients on the potential efficacy of secondary HT given their baseline characteristics and to identify patients for clinical trials.

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Disclosure

All authors have no conflicts of interest.

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